A Flexible Route Towards Five-Membered Ring Imino Sugars and Their Novel 2-Deoxy-2-fluoro Analogues

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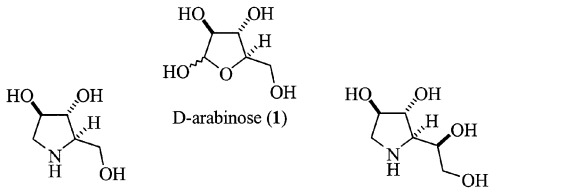
A flexible route towards five-membered ring imino sugars starting from a chiral α,β-epoxy aldehyde has been developed. The approach relies on the use of the versatile epoxyamine intermediate **4**, from which regiocontrolled epoxide opening affords diastereoselective access to trisubstituted pyrrolidines. Described here is the nucleophilic attack at C-2 of the pivotal epoxypyrrolidine **10**, leading to the biologically relevant imino sugars 1,4-dideoxy-1,4-imino-D-arabinitol (**2**) and 1,4-dideoxy-1,4-imino-L-galactitol (**3**) as well as their novel 2-deoxy-2-fluoro analogues, after oxidative manipulation of the vinyl moiety.

Introduction

Imino sugars constitute a class of carbohydrate mimetics that has already received considerable attention as major glycosidase inhibitors.[1] Considered to some extent as transition-state analogues, these alkaloids could also, in principle, interfere with the creation of glycosidic bonds. But their development as glycosyltransferase inhibitors has been limited by their intrinsic low inhibitory activity towards this class of enzymes. Over the last 10 years however, polyhydroxylated pyrrolidines and piperidines have inspired the design of novel potential glycosyltransferase inhibitors.[2] In particular, enhanced potency, as well as selectivity towards targeted enzymes, have been explored by simple *N*-substitution of these alkaloids and incorporation of key structural elements of either the natural glycosyl donor[3] or acceptor.[4] The field of therapeutic application of such compounds seems promisingly broad since they could, for example, be involved in treatment of fungal infections (chitine synthase inhibition),[5] inflammatory processes or tumor growth (α-1,3-fucosyltransferase inhibition),[6] glycosphingolipid storage disorders (ceramide glucosyltranferase inhibition),[7] and xenotransplant rejection (α-1,3-glucosyltransferase inhibition).[8]

In this context, we focused our attention on the inhibition of arabinosyltransferase activity in mycobacteria. D-Arabinose (**1**) presents indeed two advantageous characteristics: it is essential to the synthesis of the mycobacterial cell wall, and it is not normally involved in the human host metabolism. The disruption of cell wall biosynthesis resulting from the inhibition of arabinosyltransferase has been recognised as the mode of action of important antibiotics, such as the antituberculosis agent ethambutol.[9] Interestingly however, only few examples of imino sugar-derived arabinosyltransferase inhibitors have been reported.[10−12] In order to gain access to key building blocks for the design of novel arabinosyltransferase inhibitors, we decided to develop an asymmetric route to 1,4-dideoxy-1,4-imino-D-arabinitol (**2**)[13−16] a naturally-occurring broad-spectrum glycosidase inhibitor.[17] We also targeted its homologue 1,4-dideoxy-1,4-imino-L-galactitol (**3**), the D enantiomer of which is an inhibitor of the mycobacterial cell wall acting upon the incorporation of D-galactofuranose.[18,19] Finally we paid particular attention to the possibility of preparing deoxyfluoro analogues of these imino sugars, as an increased lipophilicity could be beneficial towards this membrane-located enzyme.



Results and Discussion

Following our continuous effort to develop an efficient synthetic access to imino sugars from α,β-epoxy alde-

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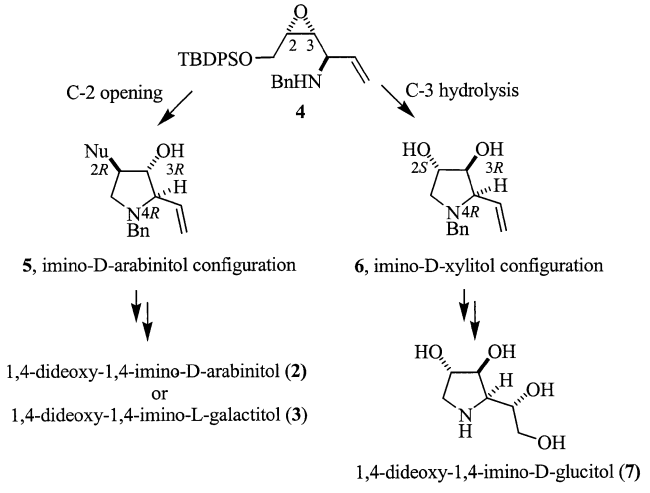
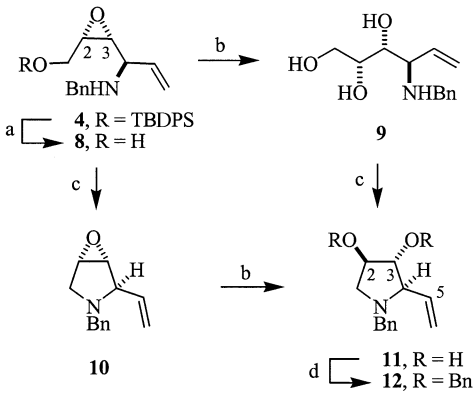
hydes,[20,21] we envisioned that the chiral epoxyamine intermediate **4** (Scheme 1) could serve as an ideal precursor for the targeted polyhydroxylated pyrrolidines. Indeed, we have already shown that regiocontrolled C-3 epoxide hydrolysis provides a route to pyrrolidine possessing the (2*S*,3*S*,4*R*)-imino-D-xylitol configuration **6** (for matter of clarity, iminoalditol carbon numbering have been used thoughout this article). This route led to an efficient asymmetric synthesis of the C_6 imino sugar 1,4-dideoxy-1,4-imino-D-glucitol (**7**). On the other hand, C-2 substitution of the same versatile epoxyamine **4** would give rise to the desired (2*R*,3*R*,4*R*)-imino-D-arabinitol stereochemical pattern **5**.



Scheme 1. Stereocontrolled access to five-membered ring imino sugars from the versatile epoxyamine **4**

We thus started studying regioselective C-2 epoxide opening. Bearing in mind that the C-1 hydroxyl could direct this process, we first chose primary alcohol **8** as a substrate (Scheme 2). The latter was readily prepared by clean desilylation of our key intermediate **4** using TBAF supported on silica gel (THF, room temp., 87% yield). We first tried to convert the 2,3-epoxy alcohol moiety into the desired triol via a base-catalysed Payne rearrangement with subsequent in situ nucleophilic trapping of the migrated epoxide.[22] Unfortunately, treatment of **8** under basic conditions (aqueous KOH, EtOH, 80 °C) resulted in complete decomposition. Another attractive option was to form a 1,2-cyclic carbonate by Lewis acid-catalysed intramolecular epoxide opening involving a phenylurethane intermediate.[23] We were however unable to prepare the latter precursor. Instead, treatment of the primary alcohol **8** with phenyl isocyanate (Et_3N, CH_2Cl_2, room temp., ca. 60% yield) afforded the cyclic ureas resulting from the *N*-acylation followed by spontaneous intramolecular C-3 nitrogen attack (isolated as a ca. 1:1 mixture of C-1 carbamate and free primary alcohol). Although irrelevant to the present study, this reaction was interestingly reminiscent of the carbonate anion oxirane opening we previously evidenced in these series.

We then turned our attention to aqueous acidic conditions. Refluxing **8** in *p*-dioxane in the presence of 3 M H_2SO_4 afforded a 70% yield of a single compound, a diastereomer of the aminotriol previously obtained through C-3 epoxide opening. Structure **9** was thus proposed for this compound and its concise transformation into the indolizidine (−)-lentiginosine unambiguously confirmed this stereochemical attribution.[21] It appeared, however, that in the context of this work, ring opening was more efficient once the pyrrolidine heterocycle had already been prepared. In Appel conditions (Ph_3P, CCl_4, Et_3N, DMF, room temp.),[24] primary alcohol was smoothly cyclised in 71% yield to epoxypyrrolidine **10**. Treatment of this derivative with aqueous H_2SO_4 in *p*-dioxane resulted in clean and highly regiocontrolled oxirane hydrolysis, affording a 94:6 mixture (estimated by ^1H NMR) of dihydroxypyrrolidines in 85% yield. The major diastereomer was separated by chromatography after standard perbenzylation (NaH, BnBr, Bu_4NI, THF, 85% yield). It was shown to be identical to a sample prepared by cyclisation of aminotriol **9** produced under the same aqueous acidic hydrolysis conditions. Therefore, it was considered to possess the desired (2*R*,3*R*,4*R*)-D-arabinitol configuration **12**, which was ultimately proven by the total syntheses of the two known imino sugars **2** and **3** (vide infra).

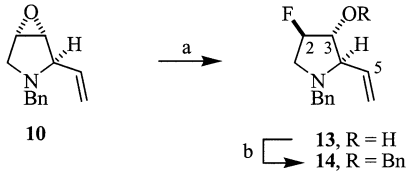


Scheme 2. a: TBAF supported on silica gel, THF, room temp., 87%; b: 3 M H_2SO_4/*p*-dioxane, reflux, 70% of **9** from **8**, 85% of a 94:6 mixture of **11** and its diastereomer from **10**; c: Ph_3P, CCl_4, Et_3N, DMF, room temp., 71% of **10** from **8**, 67% of **11** from **9**; d: NaH, BnBr, Bu_4NI, THF, 80%

At this stage, we were interested in exploiting the greater reactivity of the C-2 position towards other nucleophiles, such as fluoride anion for example. Deoxyfluoro analogues of imino sugars are indeed important compounds,[25] but there are, to the best of our knowledge, no reported examples of polyhydroxylated pyrrolidine derivatives where an on-the-ring secondary hydroxyl group has been replaced by fluorine.[26] Opening of the oxirane ring in **10** with fluoride anion would offer convenient access to such analogues.

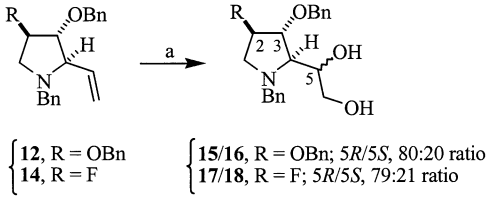
A rapid survey of the fluoride anion sources available indicated that neither TBAF nor $iPr_2NH{\cdot}3HF$ gave useful transformation when applied to **10**, even under forced conditions. More encouraging results were obtained with KHF_2. Heating at 140 °C for 5 h in ethylene glycol with a fourfold excess of reagent allowed formation of the expected fluorhydrines. Although isolated in a modest 35−40% yield, ^1H NMR of this compound revealed a re-

warding selectivity of ca. 95:5. Moreover, detailed NMR studies (COSY and HSQC 2D experiments as well as analysis of the $J_{H,F}$ and $J_{C,F}$ coupling constants) indicated that the fluorine atom had been, as desired, introduced on C-2 to afford **13** (Scheme 3). The preparation of this fluorhydrine was optimised running the reaction in commercially available HF·pyridine complex at 60 °C for 24 h.[27] This provided in 86% yield a 92:8 mixture favoring the same regioisomer **13** that could be easily separated by chromatography once benzylated under standard conditions (NaH, BnBr, Bu_4NI, THF, 83% yield) to give **14**. Stereogenicity at C-2 was assumed to be resulting of a single inversion based on the comparison of ^1H NMR spectra of benzylated C-2 fluro and hydroxy compounds **14** and **11**. These results thus opened a stereoselective access to a key intermediate in the preparation of 2-deoxy-2-fluoro analogues of polyhydroxylated pyrrolidines of the D-arabinitol configuration. It could also be potentially generalised to other nucleophiles in order to prepare diversely C-2 substituted five-membered ring imino sugars.



Scheme 3. a: HF·pyridine, 60 °C, 85% of a 92:8 mixture of **13** and its regioisomer; b: NaH, BnBr, Bu_4NI, THF, 83%

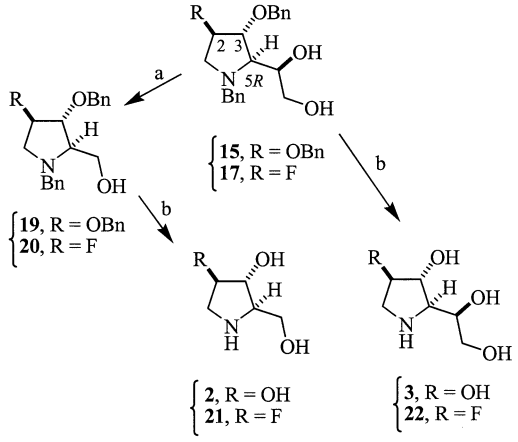
With the vinylpyrrolidine intermediates **12** and **14** in hands, we were in a position to study functionalisation of the olefin. We originally planed to prepare an epoxide intermediate, which would in turn allow derivatisation through attack at the terminal position. Unfortunately, epoxidation of olefin in **12** proved to be complicated by the presence of the neighboring basic nitrogen atom.[28] We therefore prepared diols **15** and **16** directly (69% combined yield) by standard osmylation of the double bond (OsO_4, NMO, *p*-dioxane/H_2O, 70 °C) (Scheme 4).[29] As already observed in closely related studies, the stereochemical outcome of this reaction moderately favored the *R* isomer **15** (80:20 ratio as separated compounds).[30] Interestingly, this *Si* face selectivity strongly diverge from the complete *Re* face stereocontol displayed by the D-xylitol diastereomer, suggesting a major influence of the C-3 benzyloxy group on the steric bias of these vinylpyrrolidines [the same *Si* face attack was



Scheme 4. a: OsO_4, NMO, *p*-dioxane/H_2O, 70 °C, 69% of a 80:20 mixture of **15** and **16** from **12**, 80% of a 79:21 mixture of **17** and **18** from **14**

only slightly favored (60:40 ratio) during osmylation of the related epoxypyrrolidine **10**]. The 2-deoxy-2-fluoro analogue **14** was dihydroxylated under the same conditions to produce the expected diols **17** and **18** in comparable efficiency and diastereofacial selectivity (isolated in 80% combined yield and in a 79:21 ratio). The *R* configuration was assigned to the newly formed stereocenter in the major diastereomer **17** by analogy with the studies mentioned above.

Preparation of C_5 imino sugars required oxidative cleavage of the vinyl moiety. This was more conveniently achieved from diols **15** and **17** by treatment with $NaIO_4$ followed by in situ $NaBH_4$ reduction (EtOH/H_2O, room temp., 70% yield) which led to primary alcohols **19** and **20** (Scheme 5), respectively.



Scheme 5. a: $NaIO_4$ then $NaBH_4$, EtOH/H_2O, room temp., 70% of **19** from **15**, 70% of **20** from **17**; b: Pd/C, 10 bar H_2, cat. 12 M HCl, MeOH, 94−98%

Finally, the targeted imino sugars **2** and **3**, as well as their 2-deoxy-2-fluoro analogues **21** and **22** were smoothly obtained after a debenzylation step (Pd/C, 10 bar H_2, cat. 12 M HCl, MeOH, 94−98% yield) (Scheme 5). Derivatives **2** and **3** displayed spectral and physical data in agreement with that reported in the literature.

Conclusion

In conclusion, this work illustrates the flexibility of our route to five-membered ring imino sugars from chiral α,β-epoxy aldehydes. Central to this approach is the regiocontrolled C-2 oxirane ring opening of a pivotal epoxypyrrolidine. The 2,3-dihydroxy and 2-fluoro-3-hydroxy intermediates thus prepared were used in a short synthesis of imino sugars **2** and **3**, as well as their novel 2-deoxy-2-fluoro analogues **21** and **22**, via oxidative functionalisation of the olefin. These compounds all represent valuable building blocks for the elaboration of imino sugar-derived arabinosyltransferase inhibitors. We already demonstrated that targeting of potential inhibitors of these mycobacterial enzymes can be achieved by attaching them to an acceptor-like oligoarabinofuranoside.[31]

Experimental Section

General Remarks: The following solvents and reagents were dried prior to use: carbon tetrachloride, dimethylformamide (from calcium hydride, stored over 4-Å molecular sieves), triethylamine (from calcium hydride, stored over potassium hydroxide pellets), THF (freshly distilled from sodium/benzophenone). Thin layer chromatography (TLC) reaction monitoring was carried out with Macherey−Nagel ALUGRAM® SIL G/UV$_{254}$ (0.2 mm) plates visualised with 10% phosphomolybdic acid in ethanol or Dragendorff reagent as dipping solutions. Standard column chromatography was performed with SDS 70−200 μm silica gel. Flash column chromatography was carried out with SDS 35−70 μm silica gel. Medium-pressure liquid chromatography was performed with a Jobin−Yvon apparatus using Merck 15−40 μm silica gel. NMR spectroscopic data were obtained with Bruker AC200, AC250, and AC400 instruments operating with ^{1}H spectra at 200, 250, and 400 MHz, respectively, ^{13}C spectra at 50, 63, and 100 MHz, respectively, and ^{19}F at 188 MHz (AC200). Chemical shifts are quoted in parts per million (ppm) downfield from tetramethylsilane and coupling constants are in Hertz. Infrared (IR) spectra were recorded on a Perkin−Elmer FT-IR 1725X spectrometer. Mass spectrometry (MS) data were obtained on a NERMAG R10-10 spectrometer. High resolution mass spectra (HRMS) were performed on a ThermoFinnigan MAT 95 XL spectrometer (DCI). Optical rotations were measured on a Perkin−Elmer model 141 polarimeter.

Primary Alcohol 8: TBAF on silica gel (5.70 g at ca. 1.10 mmol of fluoride/g, ca. 6.27 mmol) was added to a solution of silyl ether **4** (1.15 g, 2.51 mmol) in THF (25 mL). The reaction mixture was vigorously stirred overnight and then filtered. The silica gel was rinsed several times with ethyl acetate and the combined filtrates concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, gradient from 100:0 to 95:5) to give alcohol **8** (478 mg, 2.18 mmol, 87% yield): R_f = 0.25 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{25}$ = +9.0 (c = 1.6, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3287 (O−H), 1641 (C=C), 1032 (C-O) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40−7.20 (m, 5 H, Ph), 5.93−5.75 (m, 1 H, 5-H), 5.40−5.28 (m, 2 H, 2 × 6-H), 3.78 (AB part of an ABX, $^3J_{1\text{-H},2\text{-H}}$ = 5.1, $^3J_{1'\text{-H},2\text{-H}}$ = 6.6 Hz and $^2J_{1\text{-H},1'\text{-H}}$ = 12.3 Hz, Δδa−δb = 102.30 Hz, 2 H, 2 × 1-H), 3.73 (ABq, $^2J_{gem}$ = 12.5 Hz, Δδa−δb = 42.2 Hz, 2 H, NCH_2Ph), 3.26−3.16 (m, 2 H, 3-H and 2-H), 3.00 (dd, $^3J_{4\text{-H},3\text{-H}}$ = 4.2 Hz and $^3J_{4\text{-H},5\text{-H}}$ = 7.2 Hz, 1 H, 4-H), 2.76 (m, 2 H, O-H and N-H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.57 ($C_{quat.}$ arom.), 136.53 (C-5), 128.66, 128.51, 127.52 (CH arom.), 119.40 (C-6), 60.60 (C-1), 59.18 (C-4), 58.55 (C-3), 56.22 (C-2), 50.47 (NCH_2Ph) ppm. MS (DCI, NH_3): m/z = 220 [M + H$^+$]. HRMS (DCI, NH_3) calcd. for $C_{13}H_{18}N_1O_2$ [M + H]$^+$ 220.1337, found 220.1334.

Epoxypyrrolidine 10: To a solution of amino alcohol **8** (220 mg, 1.00 mmol) in anhydrous DMF (4.50 mL) were successively added Ph_3P (526 mg, 2.00 mmol), CCl_4 (194 mL, 2.00 mmol) and Et_3N (0.28 mL, 2.00 mmol). After stirring overnight at room temp. under inert atmosphere, MeOH (3 mL) was added. The reaction mixture was then stirred for an additional 45 min before being concentrated to dryness under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10) to give epoxypyrrolidine **10** (143 mg, 0.71 mmol, 71% yield). R_f = 0.28 (petroleum ether/EtOAc, 90:10). $[\alpha]_D^{25}$ = +3.1 (c = 1.7, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1601 (C=C), 1264 (C−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31−7.26 (m, 5 H, Ph), 5.81−5.72 (m, 1 H, 5-H), 5.35 (ddd, $^4J_{6\text{-H},4\text{-H}}$ = 1.3, $^2J_{6\text{-H},6'\text{-H}}$ = 1.8 Hz and $^3J_{6\text{-H},5\text{-H}}$ = 18.4 Hz, 1 H, 6-H) 5.22 (ddd, $^4J_{6'\text{-H},4\text{-H}}$ = 1.2, $^2J_{6'\text{-H},6\text{-H}}$ = 1.8 Hz and $^3J_{6'\text{-H},5\text{-H}}$ = 10.3 Hz, 1 H, 6′-H), 3.80 (ABq, $^2J_{gem}$ = 13.7 Hz, Δδa−δb = 23.8 Hz, 2 H, NCH_2Ph), 3.69−3.65 (m, 2 H, 2-H and 4-H), 3.55 (d, $^3J_{3\text{-H},4\text{-H}}$ = 2.9 Hz, 1 H, 3-H), 3.00 (s, 2 H, 2 × 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.03 ($C_{quat.}$ arom.), 135.11 (C-5), 128.60, 128.39, 127.09 (CH arom.), 117.64 (C-6), 66.33 (C-4), 60.57 (C-3), 60.11 (C-1), 57.31 (C-2), 53.26 (NCH_2Ph) ppm. MS (DCI, NH_3): m/z = 202 [M + H]$^+$ (100). HRMS (DCI, NH_3) calcd. for $C_{13}H_{16}NO$ [M + H]$^+$ 202.1232, found 202.1239.

Diol 11: 3 M aqueous H_2SO_4 (6.50 mL, 19.50 mmol) was added to a solution of epoxypyrrolidine **10** (390 mg, 1.94 mmol) in *p*-dioxane (8 mL). This mixture was refluxed for 5 h and allowed to cool before neutralisation with 3 M aqueous NaOH (21.00 mL) followed by solid $NaHCO_3$. *p*-Dioxane was then evaporated off under reduced pressure and the resulting aqueous phase extracted with CH_2Cl_2 (3 × 100 mL) and with EtOAc (2 × 50 mL). The combined organic phases were successively washed with water and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel treated with 2.5% v/v Et_3N (petroleum ether/EtOAc, gradient from 70:30 to 40:60) to give 94:6 mixture of diastereomeric dihydroxypyrrolidines **11** and **6** (362 mg, 1.65 mmol, 85% yield). A sample of major diastereomer **11** prepared by Appel cyclisation of aminotriol **9** was used for characterisation. R_f = 0.28 (petroleum ether/EtOAc, 90:10). IR (neat): $\tilde{\nu}_{max}$ = 3418 (O−H), 1609 (C=C), 1035 (C−O) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$/D_2O): δ = 7.16−7.08 (m, 5 H, Ph), 5.74−5.61 (m, 1 H, 5-H), 5.25−5.14 (m, 2 H, 2 × 6-H), 3.83−3.78 (m, 1 H, 3-H), 3.63 (dd, $^3J_{2\text{-H},3\text{-H}}$ = 3.3 Hz and $^3J_{2\text{-H},1'\text{-H}}$ = 7.1 Hz, 1 H, 2-H), 3.40 (AB$_q$, $^2J_{gem}$ = 11.9 Hz, Δδ$_a$−δ$_b$ = 205.4 Hz, 2 H, NCH_2Ph), 2.64 (d, $^2J_{1\text{-H},1'\text{-H}}$ = 10.8 Hz, 1 H, 1-H), 2.61−2.55 (m, 1 H, 4-H), 2.44 (dd, $^3J_{1'\text{-H},2\text{-H}}$ = 7.0 Hz and $^2J_{1'\text{-H},1\text{-H}}$ = 10.8 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$/D_2O): δ = 137.47 (C-5), 137.38 ($C_{quat.}$ arom.), 129.06, 128.09, 127.03 (CH arom.), 119.30 (C-6), 83.28 (C-3), 76.27 (C-2), 74.49 (C-4), 58.78 (NCH_2Ph), 57.53 (C-1) ppm. MS (DCI, NH_3): m/z = 220 [M + H]$^+$ (100). HRMS (DCI, NH_3) calcd. for $C_{13}H_{18}NO_2$ [M + H]$^+$ 220.1337, found 220.1335.

Dibenzyl Ether 12: NaH (80 mg of a 60% suspension in oil, 2.05 mmol) was added to a stirred solution of dihydroxypyrrolidines **11** and **6** (300 mg, 1.37 mmol) in anhydrous THF at 0 °C under inert atmosphere. After gas evolution had ceased, the reaction mixture was allowed to warm up to room temp. and tetrabutylammonium iodide (25 mg, 0.07 mmol) was added, followed after 5 min by benzyl bromide (240 μL, 2.05 mmol). The mixture was stirred at room temp. until TLC analysis showed that no starting material remained (ca. 3 h 30) and the reaction was quenched by addition of water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were successively washed with water and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by medium pressure column chromatography on silica gel (petroleum ether/CH_2Cl_2/Et_2O, 69:25:6) to give **12** (437 mg, 1.09 mmol, 80% yield) and the dibenzylated minor diastereomer (28 mg, 0.07 mmol, 5% yield). Major diastereomer **12**: R_f = 0.25 (petroleum ether/EtOAc, 90:10). $[\alpha]_D^{25}$ = −94.7 (c = 0.95, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1624 (C=C), 1097 (C−O) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.43−7.22 (m, 15 H, Ph), 6.04−5.89 (m, 1 H, 5-H), 5.44 (dd, $^2J_{6\text{-H},6'\text{-H}}$ = 1.7 Hz and $^3J_{6\text{-H},5\text{-H}}$ = 17.2 Hz, 1 H, 6-H), 5.33 (dd, $^2J_{6'\text{-H},6\text{-H}}$ = 1.7 Hz and $^3J_{6'\text{-H},5\text{-H}}$ = 10.2 Hz, 1 H, 6′-H), 4.60 (AB$_q$, $^2J_{gem}$ = 11.8 Hz, Δδ$_a$−δ$_b$ = 17.2 Hz, 2 H, OCH_2Ph), 4.47 (AB$_q$, $^2J_{gem}$ = 12.1 Hz, Δδ$_a$−δ$_b$ = 26.3 Hz, 2 H,

OCH_2Ph), 3.98−3.91 (m, 2 H, 2-H and 3-H), 3.60 (AB$_q$, $^2J_{gem}$ = 13.3 Hz, Δδa−δb = 224.2 Hz, 2 H, NCH_2Ph), 3.05 (d, $^2J_{1\text{-}H,1'\text{-}H}$ = 10.7 Hz, 1 H, 1-H), 2.94 (*pseudo*-t, $^3J_{4\text{-}H,5\text{-}H}$ = $^3J_{4\text{-}H,3\text{-}H}$ = 7.6 Hz, 1 H, 4-H), 2.47 (dd, $^3J_{1'\text{-}H,2\text{-}H}$ = 6.2 Hz, and $^2J_{1'\text{-}H,1\text{-}H}$ = 10.7 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 139.06 (C-5), 138.63, 138.43 ($C_{quat.}$ arom.), 129.16, 128.61, 128.48, 128.09, 128.03, 127.91, 127.89, 127.20 (CH arom.), 119.46 (C-6), 89.57 (C-3), 82.25 (C-2), 73.37 (C-4), 72.34 (OCH$_2$Ph), 71.36 (OCH$_2$Ph), 57.60 (NCH$_2$Ph), 56.95 (C-1) ppm. MS (DCI, NH_3): *m*/*z* = 400 [M + H$^+$] (100). HRMS (DCI, NH_3) calcd. for $C_{27}H_{30}NO_2$ [M + H]$^+$ 400.2276, found 400.2274.

Fluorohydrine 13: A solution of epoxypyrrolidine **10** (250 mg, 1.24 mmol) in commercially available HF·pyridine was heated to 60 °C with vigorous stirring for 24 h. The reaction mixture was then neutralised with solid $NaHCO_3$ and concentrated to dryness under reduced pressure. The resulting residue was extracted with CH_2Cl_2 (3 × 60 mL) and the combined organic phases were successively washed with water and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 92:8) to give fluorohydrine **13** and its regioisomer (234 mg, 1.06 mmol, 85% yield) as a 92:8 mixture. A ca. 95:5 mixture obtained by treatment with KHF_2 was used for characterisation of the major compound **13**. R_f = 0.27 (petroleum ether/EtOAc, 92:8). IR (neat): $\tilde{\nu}_{max}$ = 3413 (O−H), 1638 (C=C), 1422 (C−F), 1076 (C−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.27 (m, 5 H, Ph), 5.92−5.86 (m, 1 H, 5-H), 5.43 (ddd, $^4J_{6\text{-}H,4\text{-}H}$ = 0.7, $^2J_{6\text{-}H,6'\text{-}H}$ = 1.6, $^3J_{6\text{-}H,5\text{-}H}$ = 17.2 Hz, 1 H, 6-H), 5.37 (ddd, $^4J_{6'\text{-}H,4\text{-}H}$ = 0.4, $^2J_{6'\text{-}H,6\text{-}H}$ = 1.6 Hz, and $^3J_{6'\text{-}H,5\text{-}H}$ = 10.1 Hz, 1 H, 6′-H), 4.89 (dddd, $^3J_{2\text{-}H,1\text{-}H}$ = 1.2, $^3J_{2\text{-}H,3\text{-}H}$ = 2.3, $^3J_{2\text{-}H,1'\text{-}H}$ = 6.2 Hz, and $^2J_{2\text{-}H,F}$ = 53.8 Hz, 1 H, 2-H), 4.16 (dddd, $^4J_{3\text{-}H,1\text{-}H}$ = 0.9, $^3J_{3\text{-}H,2\text{-}H}$ = 2.2, $^3J_{3\text{-}H,4\text{-}H}$ = 7.2 Hz, and $^3J_{3\text{-}H,F}$ = 26.3 Hz, 1 H, 3-H), 3.59 (ABq, $^2J_{gem}$ = 13.4 Hz, Δδa−δb = 333.8 Hz, 2 H, NCH_2Ph), 3.11 (dd, $^2J_{1\text{-}H,1'\text{-}H}$ = 11.9 Hz and $^3J_{1\text{-}H,F}$ = 23.4 Hz, 1 H, 1-H), 2.79 (*pseudo*-t, $^3J_{4\text{-}H,3\text{-}H}$ = $^3J_{4\text{-}H,5\text{-}H}$ = 7.8 Hz, 1 H, 4-H), 2.57 (ddd, $^3J_{1'\text{-}H,2\text{-}H}$ = 6.1, $^2J_{1'\text{-}H,1\text{-}H}$ = 12.0 Hz and $^3J_{1'\text{-}H,F}$ = 31.9 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.84 ($C_{quat.}$ arom.), 137.58 (C-5), 129.28, 129.06, 128.52, 127.37 (CH arom.), 120.37 (C-6), 97.64 (d, $^1J_{C\text{-}2,F}$ = 180.7 Hz, C-2), 82.00 (d, $^2J_{C\text{-}3,F}$ = 25.9 Hz, C-3), 74.85 (d, $^3J_{C\text{-}4,F}$ = 4.7 Hz, C-4), 57.40 (d, $^2J_{C\text{-}1,F}$ = 24.2 Hz, C-1), 57.34 (NCH$_2$Ph) ppm. ^{19}F NMR (188 MHz, $CDCl_3$/D_2O) δ = −62.93 to −62.22 (m) ppm. MS (DCI, NH_3): *m*/*z* = 222 [M + H$^+$] (100). HRMS (DCI, NH_3) calcd. for $C_{13}H_{17}FNO$ [M + H]$^+$ 222.1294, found 222.1294.

Benzyl Ether 14: NaH (127 mg of a 60% suspension in oil, 3.16 mmol) was added portionwise to a stirred solution of fluorohydrine **13** and its regioisomer (500 mg, 2.26 mmol) in anhydrous THF at 0 °C under inert atmosphere. After the gas evolution had ceased, the reaction mixture was allowed to warm up to room temp. and tetrabutylammonium iodide (29 mg, 0.08 mmol) was added, followed after 5 min by benzyl bromide (527 μL, 4.52 mmol). The mixture was stirred at room temp. until TLC analysis showed that no starting material remained (ca. 6 h) and the reaction was quenched by addition of a saturated NH_4Cl aqueous solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL) and the combined organic phases were successively washed with water and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by medium pressure column chromatography on silica gel (petroleum ether/Et_2O, 93:7) to give major compound **14** (584 mg, 1.88 mmol, 83% yield). R_f = 0.23 (petroleum ether/Et_2O, 93:7). $[\alpha]_D^{25}$ = −60.9 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1638 (C=C), 1422 (C−F), 1109 (C−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.27 (m, 10 H, Ph), 5.98−5.86 (m, 1 H, 5-H), 5.54 (dd, $^2J_{6\text{-}H,6'\text{-}H}$ = 1.2 Hz and $^3J_{6\text{-}H,5\text{-}H}$ = 17.2 Hz, 1 H, 6-H), 5.35 (d, $^2J_{6'\text{-}H,6\text{-}H}$ = 1.2 Hz and $^3J_{6'\text{-}H,5\text{-}H}$ = 10.1 Hz, 1 H, 6′-H), 4.98 (ddd, $^3J_{2\text{-}H,1'\text{-}H}$ = 1.0, $^3J_{2\text{-}H,1\text{-}H}$ = 5.5 Hz, and $^2J_{2\text{-}H,F}$ = 53.5 Hz, 1 H, 2-H), 4.66 (ABq, $^2J_{gem}$ = 11.8 Hz, Δδa−δb = 26.2 Hz, 2 H, OCH_2Ph), 4.05 (d, $^2J_{gem}$ = 13.5 Hz, 1 H, NCH_2Ph), 3.98 (dd, $^3J_{3\text{-}H,2\text{-}H}$ = 6.9 Hz and $^3J_{3\text{-}H,F}$ = 25.2 Hz, 1 H, 3-H), 3.18−3.09 (m, 2 H, 1-H and NCH_2Ph), 2.93 (*pseudo*-t, $^3J_{4\text{-}H,3\text{-}H}$ = $^3J_{4\text{-}H,5\text{-}H}$ = 7.5 Hz, 1 H, 4-H), 2.52 (ddd, $^3J_{1'\text{-}H,2\text{-}H}$ = 5.5, $^2J_{1'\text{-}H,1\text{-}H}$ = 11.9 Hz, and $^3J_{1'\text{-}H,F}$ = 34.3 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.39 ($C_{quat.}$ arom.), 138.32 (C-5), 138.01 ($C_{quat.}$ arom.), 129.04, 128.71, 128.62, 128.10, 128.05, 127.39 (CH arom.), 119.82 (C-6), 97.13 (d, $^1J_{C\text{-}2,F}$ = 181.2 Hz, C-2), 89.12 (d, $^2J_{C\text{-}3,F}$ = 25.7 Hz, C-3), 73.38 (d, $^3J_{C\text{-}4,F}$ = 4.1 Hz C-4), 72.47 (OCH$_2$Ph), 58.00 (d, $^3J_{C\text{-}1,F}$ = 23.0 Hz, C-1), 57.38 (NCH$_2$Ph) ppm. ^{19}F NMR (188 MHz, $CDCl_3$/D_2O): δ = −64.09 to − 63.37 (m) ppm. MS (DCI, NH_3): *m*/*z* = 312 [M + H$^+$] (100). HRMS (DCI, NH_3) calcd. for $C_{20}H_{23}FNO$ [M + H]$^+$ 312.1764, found 312.1763.

Diol 15: To a solution of vinyl pyrrolidine **12** (250 mg, 0.62 mmol) in *p*-dioxane/H_2O (80:20) (10 mL) were successively added NMO (90 mg, 0.80 mmol) and OsO_4 (240 μL of a 0.08 M solution in *t*BuOH, 0.020 mmol). The mixture was then heated to 70 °C until TLC analysis showed that no starting material remained (ca. 6 h) before being allowed to cool down to room temp. Solid $NaHSO_3$ (100 mg, 0.96 mmol) was then added and stirring was maintained for a further 45 min at room temp. The resulting suspension was then filtered through celite and concentrated to dryness under reduced pressure. The crude product was first filtred over silica gel at atmospheric pressure (petroleum ether/EtOAc, gradient from 70:30 to 40:60) and purified by medium pressure column chromatography on silica gel (petroleum ether/CH_2Cl_2/Et_2O/*t*BuOH, gradient from 38:50:10:2 to 35:50:10:5) to give diols **15** (148 mg, 0.34 mmol, 55% yield) and **16** (37 mg, 0.085 mmol, 14% yield). R_f = 0.22 (major product), 0.20 (minor product) (petroleum ether/CH_2Cl_2/Et_2O/*t*BuOH, 38:50:10:2). Major diastereomer **15**. $[\alpha]_D^{25}$ = −41.4 (*c* = 0.6, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3423 (O−H), 1093 (C−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.30 (m, 15 H, Ph), 4.52 (ABq, $^2J_{gem}$ = 11.5 Hz, Δδa−δb = 14.3 Hz, 2 H, OCH_2Ph), 4.50 (ABq, $^2J_{gem}$ = 12.0 Hz, Δδa−δb = 22.5 Hz, 2 H, OCH_2Ph), 4.18 (d, $^3J_{3\text{-}H,4\text{-}H}$ = 4.3 Hz, 1 H, 3-H), 4.05−4.00 (m, 1 H, 5-H), 3.95 (d, $^3J_{2\text{-}H,1'\text{-}H}$ = 5.0 Hz, 1 H, 2-H), 3.74 (AB of an ABX, $^3J_{6\text{-}H,5\text{-}H}$ = 5.1, $^3J_{6'\text{-}H,5\text{-}H}$ = 6.4 Hz, and $^2J_{6\text{-}H,6'\text{-}H}$ = 11.5 Hz, Δδa−δb = 30.6 Hz, 2 H, 2 × 6-H), 3.79 (ABq, $^2J_{gem}$ = 13.2 Hz, Δδa−δb = 291.0 Hz, 2 H, NCH_2Ph), 3.14 (d, $^2J_{1\text{-}H,1'\text{-}H}$ = 10.8 Hz, 1 H, 1-H), 2.83 (dd, $^3J_{4\text{-}H,5\text{-}H}$ = 2.8 Hz and $^3J_{4\text{-}H,3\text{-}H}$ = 4.2 Hz, 1 H, 4-H), 2.63 (dd, $^3J_{1'\text{-}H,2\text{-}H}$ = 5.0 Hz and $^2J_{1'\text{-}H,1\text{-}H}$ = 10.8 Hz, 2 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.21, 137.90, 137.74 ($C_{quat.}$ arom.), 128.99, 128.77, 128.72, 128.25, 128.20, 128.06, 127.55 (CH arom.), 83.50 (C-3), 80.45 (C-2), 72.02 (OCH$_2$Ph), 71.64 (C-4), 71.14 (OCH$_2$Ph), 69.08 (C-5), 64.65 (C-6), 58.60 (NCH$_2$Ph), 56.92 (C-1) ppm. MS (DCI, NH_3): *m*/*z* = 434 [M + H$^+$] (100). HRMS (DCI, NH_3) calcd. for $C_{27}H_{32}NO_4$ [M + H]$^+$ 434.2331, found 434.2330.

Diol 17: To a solution of vinyl pyrrolidine **14** (420 mg, 1.35 mmol) in *p*-dioxane/H_2O (75:25) (20 mL) were successively added NMO (240 mg, 2.04 mmol) and OsO_4 (1.38 mL of a 0.05 M solution in *t*BuOH, 0.07 mmol). The mixture was then heated to 60 °C until TLC analysis showed that no starting material remained (ca. 5 h) before being allowed to cool to room temp. Solid $NaHSO_3$ (200 mg, 1.92 mmol) was then added and stirring was maintained

for a further 30 min at room temp. The resulting suspension was then filtered through celite and concentrated to dryness under reduced pressure. The crude product was first filtered through silica gel at atmospheric pressure (petroleum ether/EtOAc, 85:15) and purified by medium pressure column chromatography on silica gel (petroleum ether/CH_2Cl_2/Et_2O/*t*BuOH, gradient from 38:50:10:2 to 35:50:10:5) to give diols **17** (296 mg, 0.86 mmol, 63% yield) and **18** (78 mg, 0.23 mmol, 17% yield). R_f = 0.21 (major product), 0.20 (minor product) (petroleum ether/CH_2Cl_2/Et_2O/*t*BuOH, 38:50:10:2). Major diastereomer **17**. $[\alpha]_D^{25} = -22.5$ (c = 1.05, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3431 (O−H), 1637 (C=C), 1450 (C−F), 1095 (C−O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43−7.27 (m, 10 H, Ph), 4.98 (dd, $^3J_{2\text{-}H,1'\text{-}H}$ = 4.8 Hz and $^2J_{2\text{-}H,F}$ = 52.4 Hz, 1 H, 2-H), 4.62 (ABq, $^2J_{gem}$ = 11.6 Hz, Δδa−δb = 39.6 Hz, 2 H, OCH_2Ph), 4.26 (dd*pseudo*-t, $^3J_{3\text{-}H,2\text{-}H}$ = $^4J_{3\text{-}H,1\text{-}H}$= 1.2, $^3J_{3\text{-}H,4\text{-}H}$ = 5.2 Hz, and $^3J_{3\text{-}H,F}$ = 21.2 Hz, 1 H, 3-H), 4.06 (ddd, $^3J_{5\text{-}H,4\text{-}H}$ = 2.8, $^3J_{5\text{-}H,6'\text{-}H}$ = 5.2 Hz, and $^3J_{5\text{-}H,6\text{-}H}$ = 6.6 Hz, 1 H, 5-H), 3.74 (ABq, $^2J_{gem}$ = 13.6 Hz, Δ δa−δb = 311.0 Hz, 2 H, NCH_2Ph), 3.70 (AB of an ABX, $^3J_{6'\text{-}H,5\text{-}H}$ = 5.2, $^3J_{6\text{-}H,5\text{-}H}$ = 6.6 Hz, and $^2J_{6\text{-}H,6'\text{-}H}$ = 11.6 Hz, Δδa−δb = 30.4 Hz, 2 H, 2 × 6-H), 3.21 (brdd, $^2J_{1\text{-}H,1'\text{-}H}$ = 11.6 Hz and $^3J_{1\text{-}H,F}$ = 20.8 Hz, 1 H, 1-H), 2.76 (dd, $^3J_{4\text{-}H,5\text{-}H}$ = 2.8 Hz and $^3J_{4\text{-}H,3\text{-}H}$ = 5.2 Hz, 1 H, 4-H), 2.68 (ddd, $^3J_{1'\text{-}H,2\text{-}H}$ = 4.8, $^2J_{1'\text{-}H,1\text{-}H}$ = 12.0 Hz, and $^3J_{1'\text{-}H,F}$ = 36.0 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.61, 137.25 ($C_{quat.}$ arom.), 129.11, 129.04, 129.00, 128.68, 127.96 (CH arom.), 94.42 (d, $^1J_{C\text{-}2,F}$ = 182.0 Hz, C-2), 83.46 (d, $^2J_{C\text{-}3,F}$ = 27.2 Hz, C-3), 72.72 (OCH_2Ph), 71.45 (d, $^3J_{C\text{-}4,F}$ = 2.4 Hz, C-4), 68.31(C-5), 64.31(C-6), 58.42 (d, $^2J_{C\text{-}1,F}$ = 22.7 Hz, C-1), 58.13 (NCH_2Ph) ppm. ^{19}F NMR (188 MHz, $CDCl_3$/D_2O): δ = −60.62 to − 59.92 (m) ppm. MS (DCI, NH_3): m/z = 346 [M + H^+] (100). HRMS (DCI, NH_3) calcd. for $C_{20}H_{24}FNO_3$ [M + H]$^+$ 346.1818, found 346.1818.

Primary Alcohol 19: $NaIO_4$ (40 mg, 1.05 mmol) was added to a solution of diol **15** (150 mg, 0.69 mmol) in EtOH/H_2O (80:20) (8 mL). The mixture was stirred at room temp. until TLC analysis showed that no starting material remained (ca. 1 h 30 min) and then cooled to 0 °C before addition of $NaBH_4$ (77 mg, 2.05 mmol). Stirring was maintained at this temperature for 30 min and the mixture allowed to react at room temp. for 4 h. The reaction was then quenched by addition of a saturated aqueous solution of NH_4Cl, the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were successively washed with water and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 80:20) to give alcohol **19** (97 mg, 0.24 mmol, 70% yield). R_f = 0.20 (petroleum ether/EtOAc, 80:20). $[\alpha]_D^{25} = -23.4$ (c = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3441 (O−H), 1103 (C−O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.30 (m, 15 H, Ph), 4.57 (ABq, $^2J_{gem}$ = 11.7 Hz, Δδa−δb = 16.5 Hz, 2 H, OCH_2Ph), 4.49 (s, 2 H, OCH_2Ph), 4.14 (d, $^3J_{3\text{-}H,4\text{-}H}$ = 4.5 Hz, 1 H, 3-H), 3.94 (d, $^3J_{2\text{-}H,1'\text{-}H}$ = 5.2 Hz, 1 H, 2-H), 3.74 (AB of ABX, $^3J_{5\text{-}H,4\text{-}H}$ = 1.9, $^3J_{5'\text{-}H,4\text{-}H}$ = 3.1 Hz and $^2J_{5\text{-}H,5'\text{-}H}$ = 11.2 Hz, Δδa−δb = 42.7, 2 H, 2 × 5-H), 3.73 (ABq, $^2J_{gem}$ = 13.2 Hz, Δδa−δb = 242.0 Hz, 2 H, NCH_2Ph), 3.14 (d, $^2J_{1\text{-}H,1'\text{-}H}$ = 10.7 Hz, 1 H, 1-H), 2.81 (m, 1 H, 4-H), 2.67 (dd, $^3J_{1'\text{-}H,2\text{-}H}$ = 5.2 Hz and $^2J_{1'\text{-}H,1\text{-}H}$ = 10.7 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/D_2O): δ = 138.41, 138.15, 138.11 ($C_{quat.}$ arom.), 128.95, 128.71, 128.66, 128.07, 128.02, 127.97, 127.93, 127.48 (CH arom.), 85.57 (C-3), 80.75 (C-2), 72.19 (OCH_2Ph), 71.12 (OCH_2Ph), 70.64 (C-4), 59.88 (C-5), 58.20 (NCH_2Ph), 57.37 (C-1) ppm. MS (DCI, NH_3): m/z = 404 [M + H^+] (100). HRMS (DCI, NH_3) calcd. for $C_{26}H_{30}NO_3$ [M + H]$^+$ 404.2225, found 404.2227.

Primary Alcohol 20: $NaIO_4$ (50 mg, 1.30 mmol) was added to a solution of diol **17** (300 mg, 0.87 mmol) in EtOH/H_2O (80:20) (15 mL). The mixture was stirred at room temp. until TLC analysis showed that no starting material remained (ca. 1 h 20 min) and then cooled to 0 °C before addition of $NaBH_4$ (98 mg, 2.61 mmol). Stirring was maintained at this temperature for 30 min and the mixture was allowed to react at room temp. for 4 h. Reaction was then quenched by addition of a saturated aqueous solution of NH_4Cl (3 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL) and the combined organic phases were successively washed with water and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by medium pressure column chromatography on silica gel (petroleum ether/EtOAc, 85:15) to give alcohol **20** (192 mg, 0.48 mmol, 70% yield). R_f = 0.23 (petroleum ether/EtOAc, 85:15). $[\alpha]_D^{25} = -7.4$ (c = 1.0, MeOH). IR (neat): $\tilde{\nu}_{max}$ = 3412 (O−H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/D_2O): δ = 7.44−7.28 (m, 10 H, Ph), 4.99 (dd*pseudo*-t, $^3J_{2\text{-}H,3\text{-}H}$ =$^3J_{2\text{-}H,1\text{-}H}$ = 1.0, $^3J_{2\text{-}H,1'\text{-}H}$ = 4.8 Hz, and $^2J_{2\text{-}H,F}$ = 52.4 Hz, 1 H, 2-H), 4.67 (ABq, $^2J_{gem}$ = 11.6 Hz, Δδa−δb = 36.0 Hz, 2 H, OCH_2Ph), 4.25 (dd*pseudo*-t, $^3J_{3\text{-}H,2\text{-}H}$ = $^4J_{3\text{-}H,1\text{-}H}$ = 1.4, $^3J_{3\text{-}H,4\text{-}H}$ = 5.4 Hz, and $^3J_{3\text{-}H,F}$ = 21.6 Hz, 1 H, 3-H), 3.76 (AB of ABX, $^3J_{5'\text{-}H,4\text{-}H}$ = 2.0, $^3J_{5\text{-}H,4\text{-}H}$ = 3.4 Hz, and $^2J_{5\text{-}H,5'\text{-}H}$ = 11.6 Hz, Δδa−δb = 55.6 Hz, 2 H, 2 × 5-H), 3.72 (ABq. $^2J_{gem}$ = 13.2 Hz, Δδa−δb = 268.5 Hz, 2 H, NCH_2Ph), 3.24 (brdd, $^2J_{1'\text{-}H,1\text{-}H}$ = 11.8 Hz and $^3J_{1\text{-}H,F}$ = 20.8 Hz, 1 H, 1-H), 2.76−2.73 (m, 1 H, 4-H), 2.72 (ddd, $^3J_{1'\text{-}H,2\text{-}H}$ = 4.8, $^2J_{1'\text{-}H,1\text{-}H}$ = 12.0 Hz, and $^3J_{1'\text{-}H,F}$ = 35.6 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/D_2O): δ = 138.08, 137.91 ($C_{quat.}$ arom.), 129.10, 128.98, 128.97, 128.59, 128.45, 128.28, 127.87 (CH arom.), 94.88 (d, $^1J_{C\text{-}2,F}$ = 180.3 Hz, C-2), 85.62 (d, $^2J_{C\text{-}3,F}$ = 27.0 Hz, C-3), 72.78 (OCH_2Ph), 70.72 (d, $^3J_{C\text{-}4,F}$ = 2.7 Hz, C-4), 59.45(C-5), 58.57 (d, $^2J_{C\text{-}1F}$ = 22.7 Hz, C-1), 57.97 (NCH_2Ph) ppm. MS (DCI, NH_3): m/z = 316 [M + H^+] (100). HRMS (DCI, NH_3) calcd. for $C_{19}H_{23}FNO_2$ [M + H]$^+$ 316.1713, found 316.1712.

1,4-Dideoxy-1,4-imino-D-arabinitol (2): A solution of **19** (200 mg, 0.49 mmol) in MeOH (4 mL) containing 12 M HCl (3 drops) and 10% Pd/C (60 mg) was allowed to react under an H_2 atmosphere (10 bar) with stirring. After 72 h, the reaction mixture was filtered through celite and concentrated to dryness under reduced pressure. The crude product was dissolved in H_2O/MeOH (67:33) (10 mL), acidic resin (Dowex 50 WX8, 100−200 mesh, 5 g) was added, and the suspension was stirred slowly for 1 h before being filtered. The resin was successively rinsed with water (200 mL) and methanol (50 mL), taken up in 2.5 N aqueous NH_4OH (20 mL) and the mixture stirred slowly for 1 h. The suspension was then filtered and the resin rinsed with 2.5 M aqueous NH_4OH (200 mL). The resulting solution was lyophilized and the residue obtained was purified by flash column chromatography on silica gel treated with 2.5% v/v Et_3N, (CH_2Cl_2/MeOH/EtOH/NH_4OH, gradient from 50:20:20:10 to 65:5:20:10) to give **2** (62 mg, 0.47 mmol, 94% yield). R_f = 0.27 (CH_2Cl_2/MeOH/EtOH/NH_4OH, 25:10:10:5). $[\alpha]_D^{25} = +7.8$ (c = 1.0, H_2O), ref.[14] $[\alpha]_D^{25} = +8.2$ (c = 0.25, H_2O). IR (neat): $\tilde{\nu}_{max}$ = 3395 (O−H and N−H) cm^{-1}. ^1H NMR (400 MHz, CD_3OD/D_2O): δ = 4.23−4.20 (m, 1 H, 2-H), 4.00−3.99 (m, 1 H, 3-H), 3.86 (AB of ABX, $^3J_{5\text{-}H,4\text{-}H}$= 4.8, $^3J_{5'\text{-}H,4\text{-}H}$ = 9.2 Hz, and $^2J_{5\text{-}H,5'\text{-}H}$ = 11.6 Hz, Δδa−δb = 38.5 Hz, 2 H, 2 × 5-H), 3.54 (ddd, $^3J_{4\text{-}H,3\text{-}H}$ = 2.8, $^3J_{4\text{-}H,5\text{-}H}$ = 4.8 Hz, and $^2J_{4\text{-}H,5'\text{-}H}$ = 9.2 Hz, 1 H, 4-H), 3.49 (dd, $^3J_{1\text{-}H,2\text{-}H}$ = 4.0 Hz and $^2J_{1\text{-}H,1'\text{-}H}$ = 11.6 Hz, 1 H, 1-H), 3.30 (d*pseudo*-t, $^3J_{1'\text{-}H,2\text{-}H}$ = $^4J_{1'\text{-}H,3\text{-}H}$ = 0.8 Hz, and $^2J_{1'\text{-}H,1\text{-}H}$ = 11.6 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, CD_3OD/D_2O): δ = 76.48 (C-3), 75.17 (C-2), 68.84 (C-4), 59.87 (C-5), 50.92 (C-1) ppm. MS (DCI, NH_3): m/z = 134 [M + H^+] (100). HRMS (DCI, NH_3) calcd. for $C_5H_{12}NO_3$ [M + H]$^+$ 134.0817, found 134.0816.

1,4-Dideoxy-1,4-imino-L-galactitol (3): A solution of **15** (125 mg, 0.29 mmol) in MeOH (4 mL) containing 12 M HCl (3 drops) and 10% Pd/C (35 mg) was allowed to react under a H_2 atmosphere (10 bar) with stirring. After 48 h, the reaction mixture was filtered through celite and concentrated to dryness under reduced pressure. The crude product was dissolved in H_2O/MeOH (67:33) (10 mL), acidic resin (Dowex 50 WX8, 100−200 mesh, 5 g) was added, and the suspension was stirred slowly for 1 h before being filtered. The resin was successively rinsed with water (200 mL) and methanol (50 mL), taken up in 2.5 N aqueous NH_4OH (20 mL) and the mixture stirred slowly for 1 h. The suspension was then filtered and the resin rinsed with 2.5 N aqueous NH_4OH (200 mL). The resulting solution was lyophilized and the residue purified by flash column chromatography on silica gel treated with 2.5% v/v Et_3N (CH_2Cl_2/MeOH/EtOH/NH_4OH, gradient from 70:12:12:6 to 79:3:12:6) to give **3** (45 mg, 0.28 mmol, 95% yield). R_f = 0.30 (CH_2Cl_2/MeOH/EtOH/NH_4OH, 70:12:12:6). $[\alpha]_D^{25}$ = −2.40 (*c* = 3.8, H_2O), ref.[13] $[\alpha]_D^{25}$ = +3.0 (*c* = 2.4, H_2O) for the D enantiomer. IR (neat): $\tilde{\nu}_{max}$ = 3395 (O−H and N−H) cm^{-1}. ^1H NMR (400 MHz, CD_3OD/D_2O): δ = 4.10 (ddd, $^4J_{3\text{-}H,1'\text{-}H}$ = 0.8, $^3J_{3\text{-}H,4\text{-}H}$ = 4.5 Hz, and $^3J_{3\text{-}H,2\text{-}H}$ = 4.5 Hz, 1 H, 3-H), 4.08−4.05 (m, 1 H, 2-H), 3.80−3.76 (m, 1 H, 5-H), 3.44 (AB of ABX, $^3J_{6\text{-}H,5\text{-}H}$ = 4.4, $^3J_{6'\text{-}H,5\text{-}H}$ = 6.4 Hz, and $^2J_{6\text{-}H,6'\text{-}H}$ = 11.2 Hz, Δδa−δb = 22.8 Hz, 2 H, 2 × 6-H), 3.04 (AB of ABX, $^3J_{1\text{-}H,2\text{-}H}$ = 2.4, $^3J_{1'\text{-}H,2\text{-}H}$ = 4.4 Hz, and $^2J_{1\text{-}H,1'\text{-}H}$ = 12.0 Hz, Δδa−δb = 72.0 Hz, 2 H, 2 × 1-H), 3.02 (t, $^3J_{4\text{-}H,5\text{-}H}$ = $^3J_{4\text{-}H,3\text{-}H}$ = 4.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, CD_3OD/D_2O): δ = 78.18 (C-3), 77.97 (C-2), 71.57 (C-5), 67.84 (C-4), 64.48 (C-6), 52.01 (C-1) ppm. MS (DCI, NH_3): *m*/*z* = 164 [M + H^+] (100). HRMS (DCI, NH_3) calcd. for $C_6H_{14}NO_4$ [M + H]$^+$ 164.0923, found 164.0923.

Deoxyfluoro Imino Sugar 21: A solution of **20** (166 mg, 0.52 mmol) in MeOH (4 mL) containing 12 M HCl (3 drops) and 10% Pd/C (40 mg) was allowed to react under a H_2 atmosphere (10 bar) with stirring. After 48 h, the reaction mixture was filtered through celite and concentrated to dryness under reduced pressure. The crude product was dissolved in H_2O/MeOH (67:33) (10 mL), acidic resin (Dowex 50 WX8, 100−200 mesh, 5 g) was added, and the suspension was stirred slowly for 1 h before being filtered. The resin was successively rinsed with water (200 mL) and methanol (50 mL), taken up in 2.5 M aqueous NH_4OH (20 mL) and the mixture allowed to stir slowly for 1 h. The suspension was then filtered and the resin rinsed with 2.5 M aqueous NH_4OH (200 mL). The resulting solution was lyophilized and the residue purified by flash column chromatography on silica gel treated with 2.5% v/v Et_3N, (CH_2Cl_2/MeOH/EtOH/NH_4OH, gradient from 70:12:12:6 to 79:3:12:6) to give **21** (68 mg, 0.50 mmol, 97% yield). R_f = 0.30 (CH_2Cl_2/MeOH/EtOH/NH_4OH, 70:12:12:6). $[\alpha]_D^{25}$ = +18.7 (*c* = 1.0, MeOH). IR (neat): $\tilde{\nu}_{max}$ = 3395 (O−H and N−H) cm^{-1}. ^1H NMR (400 MHz, CD_3OD/D_2O): δ = 4.92 (dd*pseudo*-t, $^3J_{2\text{-}H,3\text{-}H}$ = $^3J_{2\text{-}H,1'\text{-}H}$ = 1.4, $^3J_{2\text{-}H,1\text{-}H}$ = 3.8 Hz, and $^2J_{2\text{-}H,F}$ = 52.6 Hz, 1 H, 2-H), 4.11 (dd*pseudo*-t, $^3J_{3\text{-}H,2\text{-}H}$ = $^4J_{3\text{-}H,1\text{-}H}$ = 1.2, $^3J_{3\text{-}H,4\text{-}H}$ = 4.8 Hz and $^3J_{3\text{-}H,F}$ = 21.0 Hz, 1 H, 3-H), 3.70 (AB of ABX, $^3J_{5\text{-}H,4\text{-}H}$ = 5.2, $^3J_{5'\text{-}H,4\text{-}H}$ = 6.0 Hz, and $^2J_{5\text{-}H,5'\text{-}H}$ = 11.2 Hz, Δδa−δb = 25.2 Hz, 2 H, 2 × 5-H), 3.25−3.08 (m, 2 H, 2 × 1-H), 2.98 (*pseudo*-q, $^3J_{4\text{-}H,5'\text{-}H}$ = $^3J_{4\text{-}H,5\text{-}H}$= $^3J_{4\text{-}H,3\text{-}H}$ = 5.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, CD_3OD/D_2O): δ = 99.60 (d, $^1J_{C\text{-}2,F}$ = 177.0 Hz, C-2), 77.38 (d, $^2J_{C\text{-}3,F}$ = 26.0 Hz, C-3), 67.53 (d, $^3J_{C\text{-}4,F}$ = 1.6 Hz, C-4), 61.41 (C-5), 50.72 (d, $^2J_{C\text{-}1,F}$ = 24.2 Hz, C-1) ppm. ^{19}F NMR (188 MHz, CD_3OD/D_2O): δ = −58.08 to −57.46 (m) ppm. MS (DCI, NH_3): *m*/*z* = 136 [M + H^+] (100). HRMS (DCI, NH_3) calcd. for $C_5H_{11}FNO_2$ [M + H]$^+$ 136.0774, found 136.0774.

Deoxyfluoro Imino Sugar 22: A solution of **17** (150 mg, 0.43 mmol) in MeOH (4 mL) containing 12 M HCl (3 drops) and 10% Pd/C (35 mg) was allowed to react under a H_2 atmosphere (10 bar) with stirring. After 48 h, the reaction mixture was filtered through celite and concentrated to dryness under reduced pressure. The crude product was dissolved in H_2O/MeOH (67:33) (10 mL), acidic resin (Dowex 50 WX8, 100−200 mesh, 5 g) was added, and the suspension was stirred slowly for 1 h before being filtered. The resin was successively rinsed with water (200 mL) and methanol (50 mL), taken up in 2.5 M aqueous NH_4OH (20 mL) and the mixture stirred slowly for 1 h. The suspension was then filtered and the resin rinsed with 2.5 M aqueous NH_4OH (200 mL). The resulting solution was lyophilized and the residue purified by flash column chromatography on silica gel treated with 2.5% v/v Et_3N, (CH_2Cl_2/MeOH/EtOH/NH_4OH, gradient from 70:12:12:6 to 79:3:12:6) to give **22** (68.0 mg, 0.41 mmol, 96% yield). R_f = 0.28 (CH_2Cl_2/MeOH/EtOH/NH_4OH, 70:12:12:6). $[\alpha]_D^{25}$ = +1.6 (*c* = 0.95, MeOH). IR (neat): $\tilde{\nu}_{max}$ = 3395 (O−H and N−H) cm^{-1}. ^1H NMR (400 MHz, CD_3OD/D_2O): δ = 4.92 (dd*pseudo*-t, $^3J_{2\text{-}H,3\text{-}H}$ = $^3J_{2\text{-}H,1'\text{-}H}$ = 1.2, $^3J_{2\text{-}H,1\text{-}H}$ = 3.8 Hz, and $^2J_{2\text{-}H,F}$ = 52.4 Hz, 1 H, 2-H), 4.33 (dd*pseudo*-t, $^3J_{3\text{-}H,2\text{-}H}$ = $^4J_{3\text{-}H,1\text{-}H}$ = 1.2, $^3J_{3\text{-}H,4\text{-}H}$ = 4.8 Hz, and $^3J_{3\text{-}H,F}$ = 21.4 Hz, 1 H, 3-H), 3.78−3.74 (m, 1 H, 5-H), 3.65 (AB of ABX, $^3J_{6\text{-}H,5\text{-}H}$ = 4.2, $^3J_{6'\text{-}H,5\text{-}H}$ = 6.4 Hz, and $^2J_{6\text{-}H,6'\text{-}H}$ = 11.4 Hz, Δδa−δb = 32.4 Hz, 2 H, 2 × 6-H), 3.21 (br.dd, $^2J_{1\text{-}H,1'\text{-}H}$ = 13.3 Hz and $^3J_{1\text{-}H,F}$ = 20.6 Hz, 1 H, 1-H), 3.12 (ddd, $^3J_{1\text{-}H,2\text{-}H}$ = 3.8, $^2J_{1'\text{-}H,1\text{-}H}$ = 13.3 Hz, and $^3J_{1'\text{-}H,F}$ = 35.5 Hz, 1 H, 1-H), 2.97 (*pseudo*-t, $^3J_{4\text{-}H,5\text{-}H}$ = $^3J_{4\text{-}H,3\text{-}H}$ = 5.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, CD_3OD/D_2O): δ = 99.69 (d, $^1J_{C\text{-}2,F}$ = 177.0 Hz, C-2), 76.53 (d, $^2J_{C\text{-}3,F}$ = 27.0 Hz, C-3), 71.09 (C-5), 68.09 (C-4), 64.47 (C-6), 50.84 (d, $^2J_{C\text{-}1,F}$ = 24.3 Hz, C-1) ppm. ^{19}F NMR (188 MHz, CD_3OD/D_2O): δ = −58.03 to −57.36 (m) ppm. MS (DCI, NH_3): *m*/*z* = 166 [M + H^+] (100). HRMS (DCI, NH_3) calcd. for $C_6H_{13}FNO_3$ [M + H]$^+$ 166.0879, found 166.0878.

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