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Carbohydrate derived bicyclic azetidin-3-ones as scaffolds for highly functionalized azetidines

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ABSTRACT

Bicyclic azetidin-3-ones with no acidic α-hydrogens, prepared in good yields via *cis*-2,4-di-*O*-triflates of pyranosides, are stable divergent intermediates for the synthesis of highly substituted azetidines, as illustrated by the synthesis of (2*R*,3*R*,4*R*)-3-hydroxy-4-(hydroxymethyl)-3-methylazetidine-2-carboxylic acids. Preliminary studies on the reactions of bicyclic azetidinones indicate their potential as scaffolds for novel complex azetidines.

1. Introduction

Recently, diverse azetidine scaffolds have been investigated for general bioactivity in zebra fish[1] and the development of CNS-focused libraries.[2] In the last twelve months, azetidines have been identified as components of dopamine antagonists,[3] epidermal growth factor receptor kinase inhibitors,[4] antagonists of the P2Y12 receptor,[5] and have potential for the treatment of late onset diabetes.[6] Carbohydrates are useful in accessing highly functionalized azetidines.[7–9] In particular, the β-*xylo*-**1** and β-*gluco*-**2** pyranoside ditriflates upon treatment with benzylamine gave bicyclic azetidines **3** and **4**, respectively, in 80–90% yields (Fig. 1); the α-anomers give no cyclic products.[10] The enantiomers **6L** and **6D**, the first syntheses of 3-hydroxy-2-azetidine carboxylic acids, were prepared from **3** and **4**.[11] Neither of the anomers of the *ribo* **7** and *allo* **8** epimers gave any cyclization under the same conditions; such bicyclic azetidines are only formed when all the groups are equatorial.

Azetidin-3-ones[12] provide scaffolds[13,14] including spiro building blocks[15] for the extension of chemotherapeutic space.[16] Herein we report the synthesis of stable bicyclic azetidin-3-ones **13** and **14** via the corresponding alcohols **11** and **12**. The value of **13** and **14**, with no acidic α-hydrogens, as divergent intermediates is shown by the synthesis of the amino acids **15** and **16**. Other preliminary studies on the chemistry of the azetidinones **13** and **14**, and on attempted nucleophilic displacements from the alcohol **12**, are reported.

2. Results and discussion

2.1. Synthesis of bicyclic azetidinones 13 and 14

For the synthesis of *N*-butyl azetidinone **14**, diol **17** was esterified with triflic anhydride; the resulting ditriflate **2** was treated with *n*-butylamine to afford the bicyclic azetidine **5** in 86% yield (Scheme 1). Removal of the benzyl group at C3 by transfer hydrogenation with ammonium formate in the presence of 10% palladium on carbon gave **12**, which upon subsequent oxidation by Dess–Martin periodinane led to the stable bicyclic azetidin-3-one **14** (66% from **5**; 57% from diol **17**). The C=O stretch at 1782 cm^{-1}, together with the chemical shift of C3 at 185.4 ppm, showed that ketone **14** was not hydrated.

For the *N*-benzyl ketone **13**, esterification of diol **17** with triflic anhydride, followed by reaction of the ditriflate **2** with benzylamine, gave bicyclic azetidine **4** in 72% yield.[10] Removal of both benzyl groups within **4** by transfer hydrogenation in the presence of 10% palladium on carbon gave **18**, which upon reductive amination with benzaldehyde and sodium cyanoborohydride, gave the *N*-benzyl azetidinol **11** (82%). Dess–Martin oxidation of **11** gave bicyclic ketone **13** (100%, 59% from **17**). Once more, the C=O stretch at 1786 cm^{-1} and ^{13}C chemical shift at 187.4 ppm showed a free carbonyl group at C3.

2.2. Synthesis of the amino acids 15 and 16

There is current interest in the synthesis of azetidine carboxylic acids as peptidomimetics.[17] The value of the stable bicyclic azetidinones **13** and **14** is illustrated by the synthesis of D-aminoacids **15** and **16** containing a tertiary center at C3. The synthesis of the

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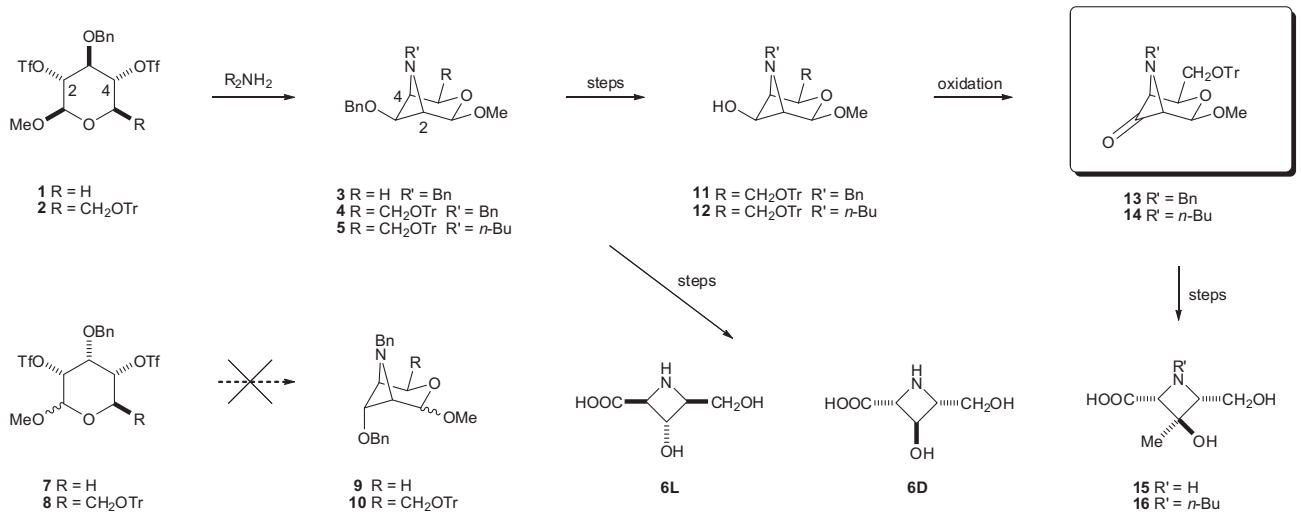
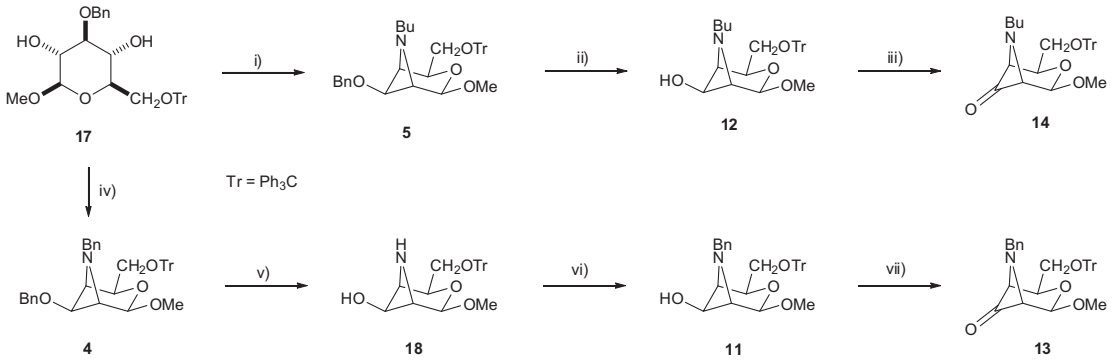


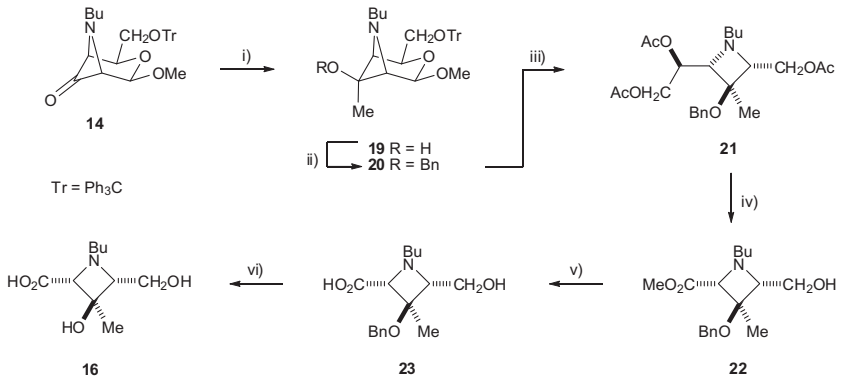
Figure 1.



Scheme 1. Synthesis of bicyclic azetidinones **13** and **14**. Reagents and conditions: (i) Tf_2O, Py, CH_2Cl_2, −10 °C, 5 h; then *n*-$BuNH_2$, CH_3CN, 70 °C, 3 h, 86% over 2 steps; (ii) Pd/C, NH_4CO_2H, MeOH, reflux, 30 min; (iii) Dess–Martin, CH_2Cl_2, rt, 20 h, 66% over 2 steps; (iv) Tf_2O, Py, CH_2Cl_2, −10 °C, 2 h; then $BnNH_2$, CH_3CN, 70 °C, 2 h, 72% over 2 steps;[10] (v) Pd/C, NH_4CO_2H, MeOH, reflux, 2 h; (vi) PhCHO, $NaBH_3CN$, 1,4-dioxane/MeOH 1:1, rt, 15 h, 82% over 2 steps; (vii) Dess–Martin, CH_2Cl_2, rt, 20 h, 100%.

N-butyl amino acid **16** was carried out by the reaction of ketone **14** with methyl lithium to afford **19** in 84% yield (Scheme 2). Analysis of the crude mixture by NMR indicated the presence of one single diastereomer. NOE analysis on **19** showed enhancements from the CH_3 group at C3 to H1 and H5, which is consistent with an axial disposition for the CH_3 group (Fig. 2).

The free hydroxyl group in **19** was protected as a benzyl ether by treatment with benzyl bromide in the presence of sodium hydride (100%). Hydrolysis of **20** with aqueous hydrochloric acid and 1,4-dioxane at 50 °C, followed by reduction with sodium borohydride and subsequent peracetylation with acetic acid and pyridine afforded D-*talo* azetidine **21** in 66% yield from **20**. Removal



Scheme 2. Synthesis of amino acid **16**. Reagents and conditions: (i) MeLi, Et_2O, −78 °C, 2 h, 84%; (ii) NaH, BnBr, DMF, rt, 18 h, 100%; (iii) 1,4-dioxane/2 M aq HCl 1:1, 50 °C, 17 h; then $NaBH_4$, MeOH, rt, 18 h; then Ac_2O, Py, rt, 17 h, 66% over 3 steps; (iv) NaOMe, MeOH, 40 °C, 16 h; then $NaIO_4$, H_2O/1,4-dioxane 3:1, 0 °C, 1 h; then I_2, K_2CO_3, MeOH, 0 °C, 2 h, 55% over 3 steps; (v) K_2CO_3, H_2O/1,4-dioxane 2:1, 65 °C, 23 h, 86%; (vi) Pd/C, H_2, 1,4-dioxane/2 M aq HCl 1:1, rt, 3 h, 100%.

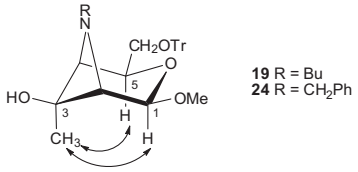


Figure 2. NOE enhancements on **19** and **24**.

of acetate groups in **21** by catalytic sodium methoxide, periodate cleavage of the C5–C6 bond in the corresponding triol, and further oxidation of the unstable aldehyde with iodine in the presence of potassium carbonate gave **22** in 55% yield over 3 steps.[11] The ester **22** was hydrolyzed by treatment with potassium carbonate at 65 °C to form **23** (86%), which on hydrogenolysis of the benzyl groups in the presence of 10% palladium on carbon afforded the azetidine carboxylic acid **16** (100%) in 26% overall yield from **14**.

Similar transformations from the *N*-benzyl bicyclic ketone **13** allowed access to the unprotected amino acid **15** in an overall yield of 45% (Scheme 3).

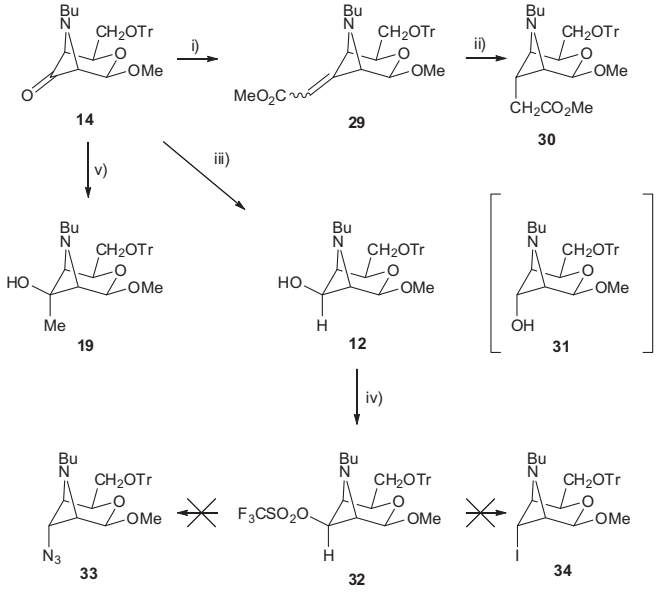
2.3. Some reactions of the bicyclic azetidinone 14

A preliminary study of reactions of *N*-butyl ketone **14** was conducted to evaluate its potential as a divergent intermediate for the synthesis of complex azetidines (Scheme 4).

(a) *Stabilized Wittig reaction.* The stabilized ylide Bu_3PCHCO_2Me reacted with **14** to afford **29** as a 1:1 mixture; subsequent hydrogenation of **29** in the presence of 10% palladium on carbon formed exclusively the azetidine **30** (51% from **14**); NOEs between the CH_2 at C3 and protons H5/H1 confirmed the axial disposition for the exocyclic fragment CH_2CO_2Me.

(b) *Reduction.* The reaction of ketone **14** with a number of different hydrides (DIBALH, $NaBH_4$, $LiEt_3BH$) always gave the equatorial alcohol **12**; no trace of the epimer **31** was observed by NMR in any of the reductions. All attempts to coordinate the hydride to the nitrogen atom to effect equatorial delivery were unsuccessful; none of the axial alcohol was formed by THF/borane. This parallels the exclusive axial addition of methyl lithium to **14** to form **19**, as reported in Scheme 2.

Since axial alcohol **31** was not available from either cyclization (Fig. 1) or by reduction of ketone **14**, we studied possible nucleophilic substitution of the alcohol at C3 in **12**. Reaction of alcohol

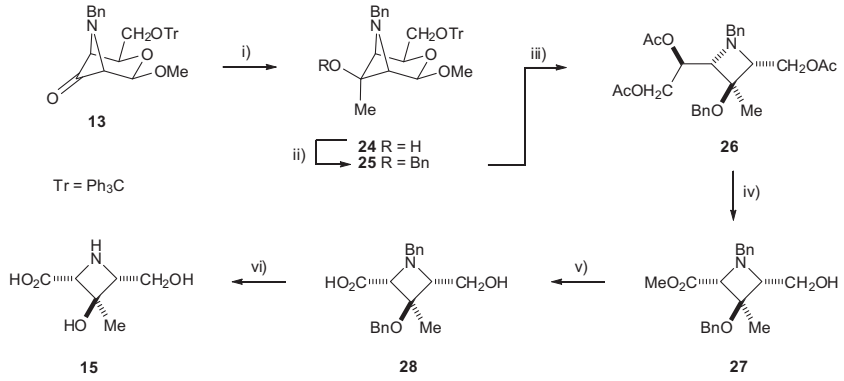


Scheme 4. Reactivity of bicyclic ketone **14**. Reagents and conditions: (i) Bu_3PCHCO_2Me, CH_2Cl_2, rt, 17 h; (ii) Pd/C, H_2, 1,4-dioxane, rt, 16 h, 51% over 2 steps; (iii) DIBAL, CH_2Cl_2 [or $NABH_4$, MeOH or $LiEt_3BH$, THF], rt, 100%; (iv) Tf_2O, Py, CH_2Cl_2, −30 °C, 1 h, 95%; (v) MeLi, Et_2O, −78 °C, 2 h, 84%.

12 with triflic anhydride gave triflate **32** in 95% yield (Scheme 4). Attempts to introduce axial groups by nucleophilic substitution using either azide or iodide in DMF to form **33** or **34** were unsuccessful. Triflate **32** was remarkably stable and did not undergo any change when heated with the nucleophiles at 60 °C overnight. Higher temperatures led to a decomposition of this material.

3. Conclusion

A convenient synthesis of the bicyclic azetidin-3-ones **13** and **14** provides stable ketones as divergent intermediates as illustrated by their efficient conversion to the amino acids **15** and **16**. Amino acid **15** is a convenient building block for its introduction as a peptidomimetic. Preliminary studies on the use of ketone **14** are reported. It was not possible to reduce **14** to an axial alcohol with a variety of reducing agents; although the equatorial alcohol **12** formed an unusually stable triflate **32**, it was not possible to introduce axial substituents by nucleophilic substitution.



Scheme 3. Synthesis of amino acid **15**. Reagents and conditions: (i) MeLi, Et_2O, rt, 18 h, 92%; (ii) NaH, BnBr, DMF, rt, 15 h, 95%; (iii) 1,4-dioxane/2 M aq HCl 1:1, 50 °C, 20 h; then $NaBH_4$, MeOH, rt, 16 h; then Ac_2O, Py, rt, 16 h, 81% over 3 steps; (iv) NaOMe, MeOH, 40 °C, 18 h; then $NaIO_4$, H_2O/1,4-dioxane 3:1, 0 °C, 50 min; then I_2, K_2CO_3, MeOH, 0 °C, 2 h, 67% over 3 steps; (v) K_2CO_3, H_2O/1,4-dioxane 3:2, 65 °C, 72 h, 95%; (vi) Pd/C, H_2, 1,4-dioxane/2 M aq HCl 1:1, rt, 14 h, 100%.

4. Experimental

4.1. General

All commercial reagents were used as supplied. DMF was purchased dry from the Aldrich chemical company in sure-seal bottles. Methanol was purchased dry from Alfa Aesar in sure-seal bottles and pyridine was purchased dry from the Fluka chemical company in sure-seal bottles over molecular sieves. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography (TLC) was performed on aluminum sheets coated with 60 F_{254} silica. Plates were visualized using a spray of 1% w/v potassium permanganate in 1 M sodium hydroxide, or a 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate solution in 2 M sulfuric acid. Flash column chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g 100 mL^{-1}. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer using thin films on a diamond ATR surface (thin film). Only the characteristic peaks are quoted. Low resolution mass spectra (m/z) were recorded on an Agilent 6120 spectrometer and high resolution mass spectra (HRMS m/z) on a Bruker micro-TOF mass analyzer using electrospray ionization (ESI). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.7 MHz) and Bruker AVIII 400 HD nanobay and Bruker DQX 400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Residual signals from the solvents were used as an internal reference, except in the case of deuterium oxide, where acetonitrile was used as the reference.

4.2. Methyl 3-*O*-benzyl-*N*-butyl-2,4-dideoxy-2,4-imino-6-*O*-trityl-β-D-talopyranoside 5

Trifluoromethanesulfonic anhydride (1.92 mL, 11.39 mmol) was added to a stirred solution of the diol **17** (2.00 g, 3.79 mmol) and pyridine (1.84 mL, 22.79 mmol) in dichloromethane (40 mL) at −10 °C under a nitrogen atmosphere. TLC analysis (2:1 cyclohexane/ethyl acetate) after 5 h indicated no starting material (R_f 0.37) and the formation of a single product (R_f 0.77). The mixture was diluted with dichloromethane (30 mL), washed with 2 M hydrochloric acid (3 × 30 mL) and the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo at 25 °C to afford **2** as a yellow oil. The crude triflate **2** was dissolved in dry acetonitrile (30 ml), after which *n*-butylamine (1.88 ml, 18.99 mmol) was added and the mixture was stirred at 70 °C under argon. TLC analysis (2:1 cyclohexane/ethyl acetate) after 3 h showed no starting material and the formation of a single product (R_f 0.56). The mixture was concentrated in vacuo and the residue purified by flash column chromatography on silica gel (6:1 cyclohexane/ethyl acetate) to afford **5** as a pale yellow oil (1.84 g, 86%); $[\alpha]_D^{20} = -16.7$ (c 0.50, $CHCl_3$); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3087, 3059, 3031, 1491, 1448 (Ar); ^{1}H NMR (500 MHz, C_6D_6): δ = 0.85 (t, J = 7.0 Hz, 3H, CH_3), 1.25–1.47 (m, 4H, 2 × CH_2), 2.96–3.00 (m, 1H, NCH_2), 3.14–3.19 (m, 1H, NCH_2), 3.27 (s, 3H, OCH_3), 3.36 (d, $J_{2,4}$ = 5.5 Hz, 1H, 2-H), 3.59 (d, $J_{4,2}$ = 5.0 Hz, 1H, 4-H), 3.63 (dd, $J_{6,6'}$ = 8.5 Hz, $J_{6,5}$ = 7.5 Hz, 1H, 6-H), 3.80 (dd, $J_{6',6}$ = 9.0 Hz, $J_{6',5}$ = 6.0 Hz, 1H, 6′-H), 3.83 (s, 1H, 3-H), 4.07 (app-t, $J_{5,6} = J_{5,6'}$ = 6.5 Hz, 1H, 5-H), 4.31 (d, J_{gem} = 12.5 Hz, 1H, OCH_2Ph), 4.34 (d, J_{gem} = 12.5 Hz, 1H, OCH_2Ph), 4.50 (s, 1H, 1-H), 7.01–7.59 (m, 20H, ArH) ppm; ^{13}C NMR (125 MHz, C_6D_6): δ = 14.4 (CH_3), 20.8 (CH_2), 31.3 (CH_2), 51.8 (NCH_2), 55.7 (OCH_3), 64.9 (C-4), 65.3 (C-6), 66.8 (C-2), 70.9 (OCH_2Ph), 76.4 (C-5), 84.4 (C-3), 87.1 (CPh_3), 101.4 (C-1), 127.3–144.8 (Ph) ppm; m/z (ESI+ve): 564 ($[M+H]^+$, 100%); HRMS m/z (ESI+ve): found 564.3097 ($[M+H]^+$); $C_{37}H_{42}NO_4$ requires 564.3108.

4.3. Methyl *N*-butyl-2,4-dideoxy-2,4-imino-6-*O*-trityl-β-D-*lyxo*-hexopyranoside-3-ulose 14

Compound **5** (760 mg, 1.35 mmol), 10% Pd on carbon (430 mg), and ammonium formate (425 mg, 6.74 mmol) were suspended in anhydrous methanol (30 mL) and the mixture was heated at reflux under argon. After 30 min, TLC analysis (1:1 cyclohexane/ethyl acetate) showed no remaining starting material (R_f 0.81) and the formation of a single product (R_f 0.14). The mixture was filtered through Celite and the path was washed with more methanol. The solvent was concentrated in vacuo to afford **12** as a colorless oil, which was dissolved in dichloromethane (10 mL), followed by the addition of Dess–Martin periodinane (1.14 g, 2.70 mmol) at 0 °C. After 20 h at rt, the mixture was diluted with dichloromethane (10 mL) and saturated aqueous sodium hydrogen carbonate (30 mL) containing sodium thiosulfate (0.12 g mL^{-1}); the reaction mixture was stirred vigorously until both phases had cleared. The layers were separated, and the organic layer washed with more of the sodium hydrogen carbonate/sodium thiosulfate solution (2 × 30 mL). The aqueous layers were back extracted with dichloromethane (15 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (7:1 cyclohexane/ethyl acetate) to afford **14** as a colorless oil (423 mg, 66% after 2 steps). $[\alpha]_D^{20} = -43.2$ (c 0.47, $CHCl_3$); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3086, 3058, 3024 (Ar), 1782 (CO); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.3 Hz, 3H, CH_3), 1.27–1.45 (m, 4H, 2 × CH_2), 2.40–2.45 (m, 1H, NCH_2), 2.50–2.56 (m, 1H, NCH_2), 3.32 (s, 3H, OCH_3), 3.43 (dd, $J_{6,6'}$ = 9.0 Hz, $J_{6,5}$ = 5.0 Hz, 1H, 6-H), 3.81–3.86 (m, 2H, 6′-H and 2-H), 4.15–4.18 (m, 1H, 5-H), 4.22 (dd, $J_{4,2}$ = 6.5 Hz, $J_{4,5}$ = 2.0 Hz, 1H, 4-H), 4.80 (d, $J_{1,2}$ = 2.5 Hz, 1H, 1-H), 7.24–7.44 (m, 15H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2 (CH_3), 20.4 (CH_2), 30.8 (CH_2), 54.4 (NCH_2), 56.1 (OCH_3), 62.4 (C-6), 76.8 (C-5), 84.9 (C-4), 86.3 (C-2), 86.9 (CPh_3), 100.2 (C-1), 127.3–144.1 (Ph), 185.4 (C-3) ppm; m/z (ESI+ve): 504 ($[M+H+CH_3OH]^+$, 100%); HRMS m/z (ESI+ve): found 504.2740 ($[M+H+CH_3OH]^+$); $C_{31}H_{38}NO_5$ requires 504.2744.

4.4. Methyl *N*-butyl-2,4-dideoxy-2,4-imino-3-methyl-6-*O*-trityl-β-D-talopyranoside 19

Methyl lithium (1.6 M in Et_2O, 1.2 mL, 1.91 mmol) was added dropwise to a stirred solution of **14** (450 mg, 0.95 mmol) in diethyl ether (10 mL) at −78 °C under an atmosphere of argon. After 2 h, TLC analysis (3:1 cyclohexane/ethyl acetate) showed complete consumption of the starting material (R_f 0.52) and the formation of a single product (R_f 0.14). The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (5:1 cyclohexane/ethyl acetate) to afford **19** as a colorless oil (391 mg, 84%). $[\alpha]_D^{20} = -50.1$ (c 0.40, $CHCl_3$); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3302 (OH), 3087, 3059, 3023, 1491, 1449 (Ar); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79 (t, J = 7.0 Hz, 3H, CH_3), 1.06–1.21 (m, 4H, 2 × CH_2), 1.28 (s, 3H, CH_3), 2.39–2.44 (m, 1H, NCH_2), 2.75–2.79 (m, 1H, NCH_2), 3.06 (dd, $J_{6,6'}$ = 8.5 Hz, $J_{6,5}$ = 7.0 Hz, 1H, 6-H), 3.26 (d, $J_{2,4}$ = 4.0 Hz, 1H, 2-H), 3.39 (d, $J_{4,2}$ = 4.0 Hz, 1H, 4-H), 3.46 (s, 3H, OCH_3), 3.59 (dd, $J_{6',6}$ = 8.5 Hz, $J_{6',5}$ = 7.0 Hz, 1H, 6′-H), 4.06 (t, $J_{5,6} = J_{5,6'}$ = 6.5 Hz, 1H, 5-H), 4.77 (s, 1H, 1-H), 7.23–7.48 (m, 15H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3),

15.4 (CH_3), 20.4 (CH_2), 30.1 (CH_2), 47.9 (NCH_2), 56.4 (OCH_3), 65.4 (C-6), 69.7 (C-4), 71.3 (C-2), 71.9 (C-5), 76.7 (C-3), 86.7 (CPh_3), 99.4 (C-1), 127.2–143.9 (Ph) ppm; *m*/*z* (ESI+ve): 488 ($[M+H]^+$, 100%); HRMS *m*/*z* (ESI+ve): found 488.2793 ($[M+H]^+$); $C_{31}H_{38}NO_4$ requires 488.2795.

4.5. Methyl 3-*O*-benzyl-*N*-butyl-2,4-dideoxy-2,4-imino-3-methyl-6-*O*-trityl-β-D-talopyranoside 20

Sodium hydride (60% in mineral oil, 44 mg, 1.11 mmol) was added to a stirred solution of **19** (275 mg, 0.56 mmol) in anhydrous *N*,*N*-dimethylformamide (5 mL) at 0 °C under an argon atmosphere. Benzyl bromide (0.13 mL, 1.11 mmol) was added dropwise, and the resulting suspension stirred at rt. After 18 h, TLC analysis (1:1 cyclohexane/ethyl acetate) showed no remaining starting material (R_f 0.21) and the formation of a single product (R_f 0.78). The reaction mixture was partitioned between ethyl acetate (20 mL) and 50% brine (20 mL). The organic layer was washed with 50% brine (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the crude product as a yellow oil. Purification by flash column chromatography on silica gel (6:1 cyclohexane/ethyl acetate) afforded **20** as a pale yellow oil (325 mg, 100%). $[\alpha]_D^{20} = -34.3$ (*c* 0.44, CH_2Cl_2); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3087, 3060, 3031, 1492, 1449 (Ar); ^1H NMR (500 MHz, CD_3CN): δ = 0.77 (t, *J* = 7.3 Hz, 3H, CH_3), 0.97–1.15 (m, 4H, 2 × CH_2), 1.36 (s, 1H, CH_3), 2.69–2.75 (m, 1H, NCH_2), 2.98–3.03 (m, 1H, NCH_2), 3.21–3.24 (m, 2H, 2-H and 6-H), 3.33 (s, 3H, OCH_3), 3.37 (dd, $J_{6',6}$ = 8.5 Hz, $J_{6',5}$ = 6.0 Hz, 1H, 6′-H), 3.41 (d, $J_{4,2}$ = 5.5 Hz, 1H, 4-H), 4.05 (t, $J_{5,6} = J_{5,6'}$ = 6.0 Hz, 1H, 5-H), 4.56 (s, 2H, OCH_2Ph), 4.69 (s, 1H, 1-H), 7.25–7.47 (m, 20H, ArH) ppm; ^{13}C NMR (125 MHz, CD_3CN): δ = 14.4 (CH_3), 15.7 (CH_3), 21.1 (CH_2), 32.1 (CH_2), 53.5 (NCH_2), 55.9 (OCH_3), 65.4 (C-6), 65.9 (OCH_2Ph), 66.4 (C-4), 68.8 (C-2), 76.3 (C-5), 87.0, 87.3 (CPh_3 and C-3), 102.0 (C-1), 128.1–145.3 (Ph) ppm; *m*/*z* (ESI+ve): 578 ($[M+H]^+$, 100%); HRMS *m*/*z* (ESI+ve): found 578.3254 ($[M+H]^+$); $C_{38}H_{44}NO_4$ requires 578.3265.

4.6. 1,5,6-Tri-*O*-acetyl-3-*O*-benzyl-*N*-butyl-2,4-dideoxy-2,4-imino-3-methyl-D-talitol 21

Compound **20** (182 mg, 0.32 mmol) was dissolved in 1:1 v/v 1,4-dioxane/2 M hydrochloric acid (18 mL) and stirred at 50 °C. After 17 h, the reaction mixture was cooled at rt, diluted with dichloromethane (50 mL), and washed with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with dichloromethane (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude lactol as a yellow oil. This material was re-dissolved in methanol (7 mL), sodium borohydride (15 mg, 0.41 mmol) added and the mixture stirred at rt. After 18 h, mass spectrometry showed no remaining starting material and the formation of a single product (*m*/*z* 324). The mixture was quenched with glacial acetic acid and concentrated in vacuo to afford the crude triol as a white solid. This was re-dissolved in 1:1 pyridine/acetic anhydride (4 mL) and stirred at rt. After 17 h, the mixture was concentrated in vacuo, co-evaporated with toluene (3 × 10 mL), and the residue purified by flash column chromatography on silica gel (6:1 to 3:1, cyclohexane/ethyl acetate) to afford **21** as a yellow oil (93 mg, 66%). $[\alpha]_D^{20} = +24.2$ (*c* 0.63, $CHCl_3$); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3066, 3030 (Ar), 1745 (OAc); ^1H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.5 Hz, 3H, CH_3), 1.22–1.44 (m, 4H, 2 × CH_2), 1.47 (s, 3H, CH_3), 2.01 (s, 3H, OAc), 2.07 (s, 6H, OAc), 2.46–2.51 (m, 1H, NCH_2), 2.72–2.77 (m, 1H, NCH_2), 3.18 (dd, $J_{2,1}$ = 8.0 Hz, $J_{2,1'}$ = 5.0 Hz, 1H, 2-H), 3.20 (d, $J_{4,5}$ = 9.5 Hz, 1H, 4-H), 3.97 (dd, $J_{6,6'}$ = 12.5 Hz, $J_{6,5}$ = 7.0 Hz, 1H, 6-H), 4.00 (dd, $J_{1,1'}$ = 11.5 Hz, $J_{1,2}$ = 8.0 Hz, 1H, 1-H), 4.17 (dd, $J_{1',1}$ = 11.5 Hz, $J_{1',2}$ = 5.0 Hz, 1H, 1′-H), 4.35 (dd, $J_{6',6}$ = 12.5 Hz, $J_{6',5}$ = 2.5 Hz, 1H, 6′-H), 4.40 (d, J_{gem} = 12.0 Hz, 1H, OCH_2Ph), 4.46 (d, J_{gem} = 12.0 Hz, 1H, OCH_2Ph), 5.23–5.27 (m, 1H, 5-H), 7.29–7.37 (m, 5H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 14.7 (CH_3), 20.7 (CH_2), 20.9, 21.1, 21.3 (3 × OAc), 30.7 (CH_2), 59.4 (NCH_2), 63.7 (C-6), 64.0 (C-1), 65.3 (OCH_2Ph), 70.6, 70.7 (C-4 and C-2), 72.2 (C-5), 76.4 (C-3), 127.4–138.5 (Ph), 170.3, 170.6, 170.9 (3 × OAc) ppm; *m*/*z* (ESI+ve): 450 ($[M+H]^+$, 100%; 472 ($[M+Na]^+$, 16%); HRMS *m*/*z* (ESI+ve): found 450.2478 ($[M+H]^+$); $C_{24}H_{36}NO_7$ requires 450.2486.

4.7. Methyl 3-*O*-benzyl-*N*-butyl-2,4-dideoxy-2,4-imino-3-methyl-D-ribonate 22

Sodium methoxide (5 mg, 0.09 mmol) was added to a stirred solution of triacetate **21** (93 mg, 0.21 mmol) in methanol (5 mL) at 40 °C. After 16 h, TLC analysis (1:1 cyclohexane/ethyl acetate) showed the formation of a single product (R_f 0.00). The mixture was concentrated in vacuo to afford the triol as a colorless oil (71 mg, quant). Sodium periodate (27 mg, 0.12 mmol) was added to a solution of the triol (31 mg, 0.09 mmol) in water (1 mL) and 1,4-dioxane (0.3 mL), and cooled at 0 °C. After 1 h at 0 °C, TLC analysis (2:8 methanol/ethyl acetate) showed the formation of the product (R_f 0.71) and unidentifiable by-products. Ethanol (10 mL) was added, the reaction mixture stirred for 10 min and the resulting precipitate was removed via filtration (GF/A glass microfibre). The filtrate was concentrated in vacuo at 20 °C to yield an unstable lactol, which was used without further purification. This was re-dissolved in anhydrous methanol (1 mL) containing potassium carbonate (40 mg, 0.29 mmol). A solution of iodine (32 mg, 0.12 mmol) in methanol (1 mL) was added dropwise and the resulting suspension was stirred at 0 °C under a nitrogen atmosphere. After 2 h, the reaction was quenched with satd aq. sodium thiosulfate and then extracted with ethyl acetate (4 × 7 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo, and the residue purified by flash column chromatography on silica gel (6:1 to 1:1, cyclohexane/ethyl acetate) to afford **22** as a colorless oil (17 mg, 55% from **21**). $[\alpha]_D^{20} = -3.5$ (*c* 0.46, $CHCl_3$); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3090, 3064, 3032 (Ar), 1748 (CO), 1498, 1454 (Ar); ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 3H, CH_3), 1.31–1.40 (m, 4H, 2 × CH_2), 1.43 (s, 3H, CH_3), 2.58–2.64 (m, 1H, NCH_2), 2.68–2.74 (m, 1H, NCH_2), 2.88 (bs, 1H, OH), 3.26 (t, $J_{4,5} = J_{4,5'}$ = 9.0 Hz, 1H, 4-H), 3.67 (d, $J_{5,4}$ = 9.0 Hz, 2H, 5-H and 5′-H), 3.76 (s, 1H, 2-H), 3.78 (s, 3H, OCH_3), 4.51 (d, J_{gem} = 11.5 Hz, 1H, OCH_2Ph), 4.60 (d, J_{gem} = 11.5 Hz, 1H, OCH_2Ph), 7.28–7.37 (m, 5H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 14.7 (CH_3), 20.6 (CH_2), 29.9 (CH_2), 52.0 (OCH_3), 57.8 (NCH_2), 59.7 (C-5), 65.5 (OCH_2Ph), 72.6 (C-4), 73.6 (C-2), 78.3 (C-3), 127.7–138.3 (Ph), 171.2 (C-1) ppm; *m*/*z* (ESI+ve): 322 ($[M+H]^+$, 100%; 344 ($[M+Na]^+$, 10%); HRMS *m*/*z* (ESI+ve): found 344.1822 ($[M+Na]^+$); $C_{18}H_{27}NNaO_4$ requires 344.1832.

4.8. 3-*O*-Benzyl-*N*-butyl-2,4-dideoxy-2,4-imino-3-methyl-D-ribonic acid 23

At first, K_2CO_3 (15 mg, 0.11 mmol) was added to a solution of **22** (17 mg, 0.05 mmol) in water (3 mL) and 1,4-dioxane (1.5 mL). The resulting mixture was stirred at 65 °C. After 23 h, mass spectrometry showed no remaining starting material and the formation of a single product (*m*/*z* 308). The solvents were removed in vacuo and the remaining residue was loaded onto a Serdolit CG-400 I strongly basic ion exchange resin. The column was flushed with water and then eluted with 2 M acetic acid. The acidic fraction was reduced in vacuo to afford **23** as a waxy solid (14 mg, 86%). $[\alpha]_D^{20} = -8.8$ (*c* 0.25, methanol); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3323 (OH), 1731 (CO); ^1H NMR (500 MHz, C_5D_5N): δ = 0.79 (t, *J* = 7.3 Hz, 3H, CH_3), 1.28–1.35 (m, 2H, CH_2), 1.66–1.73 (m, 1H,

CH_2), 1.88 (m, 4H, CH_2 and CH_3), 2.98 (m, 1H, NCH_2), 3.24 (m, 1H, NCH_2), 3.96 (bs, 1H, 4-H), 4.20 (dd, $J_{5,5'}$ = 12.0 Hz, $J_{5,4}$ = 6.5 Hz, 1H, 5-H), 4.32–4.34 (m, 1H, 5′-H), 4.48 (s, 1H, 2-H), 4.94 (d, J_{gem} = 11.5 Hz, 1H, OCH_2Ph), 5.02 (d, J_{gem} = 11.5 Hz, 1H, OCH_2Ph), 7.31–7.41 (m, 5H, ArH) ppm; ^{13}C NMR (125 MHz, C_5D_5N): δ = 15.9, 16.9 (CH_3), 22.6 (CH_2), 32.5 (CH_2), 60.6 (NCH_2), 62.5 (C-5), 68.2 (OCH_2-Ph), 76.8, 77.2 (C-2 and C-4), 80.2 (C-3), 130.2–141.4 (Ph), 173.9 (C-1) ppm; *m*/*z* (ESI+ve): 308 ([M+H]$^+$, 100%; 330 ([M+Na]$^+$, 65%); HRMS *m*/*z* (ESI+ve): found 330.1671 ([M+Na]$^+$); $C_{17}H_{25}NNaO_4$ requires 330.1676.

4.9. *N*-Butyl-2,4-dideoxy-2,4-imino-3-methyl-D-ribonic acid 16

At first, 10% Pd on carbon (6 mg) was added to a degassed solution of **23** (14 mg, 0.05 mmol) in 1,4-dioxane (1 mL) and aqueous HCl (2 m, 1 mL) and the resulting solution was stirred at room temperature under hydrogen. After 3 h, the reaction mixture was filtered (GF/A glass microfibre) and the solvents were removed in vacuo to afford **16** as a colorless oil (10 mg, quant). $[\alpha]_D^{20} = +7.0$ (*c* 0.60, methanol); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3291 (OH), 1733 (CO); ^{1}H NMR (400 MHz, D_2O): δ = 0.90 (t, *J* = 7.2 Hz, 3H, CH_3), 1.24–1.37 (m, 2H, CH_2), 1.41 (s, 3H, CH_3), 1.57–1.64 (m, 2H, CH_2), 3.25–3.32 (m, 1H, NCH_2), 3.40–3.48 (m, 1H, NCH_2), 3.99 (d, $J_{5,4}$ = 6.4 Hz, 2H, 5-H and 5′-H), 4.25 (t, $J_{4,5} = J_{4,5'}$ = 6.4 Hz, 1H, 4-H), 4.74 (s, 1H, 2-H) ppm; ^{13}C NMR (100 MHz, D_2O): δ = 13.3, 16.8 (CH_3), 19.7 (CH_2), 26.8 (CH_2), 57.1 (NCH_2 and C-5), 71.9 (C-3), 76.1 (C-2), 77.0 (C-4), 168.9 (C-1) ppm; *m*/*z* (ESI+ve): 218 ([M+H]$^+$, 100%; HRMS *m*/*z* (ESI+ve): found 240.1208 ([M+Na]$^+$); $C_{10}H_{19}NNaO_4$ requires 240.1206.

4.10. Methyl *N*-benzyl-2,4-dideoxy-2,4-imino-6-*O*-trityl-β-D-talopyranoside 11

Compound **4** (277 mg, 0.46 mmol), 10% Pd on carbon (148 mg), and ammonium formate (146 mg, 2.32 mmol) were suspended in anhydrous methanol (20 mL) and the mixture was heated at reflux under argon. After 2 h, TLC analysis (2:1 cyclohexane/ethyl acetate) showed no remaining starting material (R_f 0.65) and the formation of a single product (R_f 0.16). The mixture was filtered through Celite and the path was washed with more methanol. The solvent was concentrated in vacuo to afford **18** as a colorless oil (194 mg, quant.). The crude azetidine **18** (177 mg, 0.42 mmol) was dissolved in 1,4-dioxane (4 mL) and benzaldehyde (0.22 mL, 2.11 mmol) was added. A solution of $NaBH_3CN$ (133 mg, 2.11 mmol) in methanol (4 mL) was added, and the mixture stirred at rt. After 15 h, mass spectrometry showed the formation of a single product (*m*/*z* 508). Solvents were removed in vacuo and the resulting residue was partitioned between ethyl acetate (10 mL) and 50% brine (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (10:1 to 1:2, cyclohexane/ethyl acetate) afforded **11** as a colorless oil (177 mg, 82% after 2 steps). $[\alpha]_D^{20} = -29.8$ (*c* 0.40, methanol); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3060, 3026, 1599, 1492, 1448 (Ar); ^{1}H NMR (400 MHz, CD_3CN): δ = 2.83 (dd, $J_{6,6'}$ = 9.2 Hz, $J_{6,5}$ = 5.2 Hz, 1H, 6-H), 3.22 (d, $J_{2,4}$ = 4.6 Hz, 1H, 2-H), 3.26 (d, $J_{4,2}$ = 4.6 Hz, 1H, 4-H), 3.44 (dd, $J_{6',6}$ = 9.6 Hz, $J_{6',5}$ = 8.0 Hz, 1H, 6′-H), 3.46 (s, 3H, OCH_3), 3.79 (bs, 1H, OH), 3.93–4.02 (m, 4H, 5-H, 3-H and NCH_2), 4.79 (s, 1H, 1-H), 7.07–7.42 (m, 20H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3CN): δ = 56.4 (OCH_3), 61.0 (NCH_2), 66.6 (C-6), 68.1 (C-4), 70.5 (C-2), 75.3 (C-5), 76.9 (C-3), 87.4 (CPh_3), 101.6 (C-1), 127.3–145.1 (Ph) ppm; *m*/*z* (ESI+ve): 508 ([M+H]$^+$, 100%); HRMS *m*/*z* (ESI+ve): found 508.2474 ([M+H]$^+$); $C_{33}H_{34}NO_4$ requires 508.2482.

4.11. Methyl *N*-benzyl-2,4-dideoxy-2,4-imino-6-*O*-trityl-β-D-*lyxo*-hexopyranoside-3-ulose 13

Dess-Martin periodinane (284 mg, 0.66 mmol) was added to a solution of **11** (170 mg, 0.33 mmol) in dichloromethane (6 mL) at 0 °C. After 20 h at rt, the mixture was diluted with dichloromethane (10 mL) and saturated aqueous sodium hydrogen carbonate (10 mL) containing sodium thiosulfate (0.12 g mL^{-1}), and the mixture was stirred vigorously until both phases had cleared. The layers were separated, and the organic layer washed with more of the sodium hydrogen carbonate/sodium thiosulfate solution (10 mL). The aqueous layers were back extracted with dichloromethane (10 mL), and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. This residue was purified by flash column chromatography on silica gel (5:1 cyclohexane/ethyl acetate) to afford **13** as a colorless oil (172 mg, quant). $[\alpha]_D^{20} = -55.4$ (*c* 0.26, CH_2Cl_2); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3086, 3060, 3031 (Ar), 1786 (CO); ^{1}H NMR (400 MHz, CD_3CN): δ = 3.21 (s, 3H, OCH_3), 3.33 (dd, $J_{6,6'}$ = 8.8 Hz, $J_{6,5}$ = 5.4 Hz, 1H, 6-H), 3.61 (d, J_{gem} = 13.6 Hz, 1H, NCH_2), 3.66 (dd, $J_{6',6}$ = 8.8 Hz, $J_{6',5}$ = 8.0 Hz, 1H, 6′-H), 3.70 (d, J_{gem} = 13.6 Hz, 1H, NCH_2), 3.89 (dd, $J_{2,4}$ = 6.4 Hz, $J_{2,1}$ = 2.8 Hz, 1H, 2-H), 4.18 (dd, $J_{4,2}$ = 6.4 Hz, $J_{4,5}$ = 2.8 Hz, 1H, 4-H), 4.22–4.26 (m, 1H, 5-H), 4.82 (d, $J_{1,2}$ = 2.8 Hz, 1H, 1-H), 7.24–7.38 (m, 20H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3CN): δ = 55.9 (OCH_3), 59.1 (NCH_2), 63.8 (C-6), 77.9 (C-5), 85.5 (C-4), 86.7 (C-2), 87.6 (CPh_3), 101.3 (C-1), 128.1–145.1 (Ph), 187.4 (C-3) ppm; *m*/*z* (ESI+ve): 538 ([M+H+CH_3OH]$^+$, 100%); HRMS *m*/*z* (ESI+ve): found 538.2566 ([M+H+CH_3OH]$^+$); $C_{34}H_{36}NO_5$ requires 538.2588.

4.12. Methyl *N*-benzyl-2,4-dideoxy-2,4-imino-3-methyl-6-*O*-trityl-β-D-talopyranoside 24

Methyl lithium (1.6 M in Et_2O, 0.42 mL, 0.67 mmol) was added dropwise to a stirred solution of **13** (170 mg, 0.33 mmol) in diethyl ether (6 mL) under an atmosphere of argon. After 18 h, TLC analysis (1:1 cyclohexane/ethyl acetate) showed the complete consumption of the starting material (R_f 0.79) and the formation of a single product (R_f 0.61). The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (5:1 to 1:1, cyclohexane/ethyl acetate) to afford **24** as a colorless oil (161 mg, 92%). $[\alpha]_D^{20} = -48.5$ (*c* 0.70, CH_2Cl_2); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3086, 3059, 3029, 1492, 1449 (Ar); ^{1}H NMR (500 MHz, CD_3CN): δ = 1.20 (s, 3H, CH_3), 2.69 (dd, $J_{6,6'}$ = 9.5 Hz, $J_{6,5}$ = 4.5 Hz, 1H, 6-H), 3.14 (d, $J_{4,2}$ = 4.5 Hz, 1H, 4-H), 3.19 (d, $J_{2,4}$ = 4.5 Hz, 1H, 2-H), 3.50 (s, 3H, OCH_3), 3.52 (dd, $J_{6',6}$ = 9.5 Hz, $J_{6',5}$ = 7.5 Hz, 1H, 6′-H), 3.91 (d, J_{gem} = 14.5 Hz, 1H, NCH_2), 3.97–4.02 (m, 2H, 5-H and NCH_2), 4.15 (s, 1H, OH), 4.84 (s, 1H, 1-H), 7.04–7.43 (m, 20H, ArH) ppm; ^{13}C NMR (125 MHz, CD_3CN): δ = 16.9 (CH_3), 53.7 (NCH_2), 56.5 (OCH_3), 67.0 (C-6), 70.4 (C-4), 72.5 (C-2), 73.4 (C-5), 77.9 (C-3), 87.4 (CPh_3), 100.6 (C-1), 127.4–145.1 (Ph) ppm; *m*/*z* (ESI+ve): 522 ([M+H]$^+$, 100%); HRMS *m*/*z* (ESI+ve): found 522.2622 ([M+H]$^+$); $C_{34}H_{36}NO_4$ requires 522.2639.

4.13. Methyl *N*-benzyl-3-*O*-benzyl-2,4-dideoxy-2,4-imino-3-methyl-6-*O*-trityl-β-D-talopyranoside 25

Sodium hydride (60% in mineral oil, 10 mg, 0.41 mmol) was added to a stirred solution of **24** (107 mg, 0.21 mmol) in anhydrous *N*,*N*-dimethylformamide (3 mL) at 0 °C under an argon atmosphere. Benzyl bromide (0.05 mL, 0.41 mmol) was added dropwise, and the resulting suspension stirred at rt. After 15 h, TLC analysis (3:1 cyclohexane/ethyl acetate) showed no remaining starting

material (R_f 0.23) and the formation of a single product (R_f 0.65). The reaction mixture was partitioned between ethyl acetate (10 mL) and 50% brine (10 mL). The organic layer was washed with 50% brine (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the crude product as a yellow oil. Purification by flash column chromatography on silica gel (6:1 cyclohexane/ethyl acetate) afforded **25** as a pale yellow oil (119 mg, 95%). $[\alpha]_D^{20} = -40.7$ (*c* 0.41, CH_2Cl_2); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3086, 3060, 3029, 1493, 1449 (Ar); ^1H NMR (500 MHz, CD_3CN): δ = 1.37 (s, 3H, CH_3), 3.00 (dd, $J_{6,6'}$ = 9.0 Hz, $J_{6,5}$ = 6.3 Hz, 1H, 6-H), 3.35 (d, $J_{2,4}$ = 5.5 Hz, 1H, 2-H), 3.37 (d, $J_{4,2}$ = 5.5 Hz, 1H, 4-H), 3.41 (s, 3H, OCH_3), 3.45 (dd, $J_{6',6}$ = 9.0 Hz, $J_{6',5}$ = 6.3 Hz, 1H, 6′-H), 3.95 (t, $J_{5,6} = J_{5,6'}$ = 6.3 Hz, 1H, 5-H), 4.10 (s, 2H, NCH_2), 4.60 (s, 2H, OCH_2Ph), 4.77 (s, 1H, 1-H), 7.06–7.47 (m, 25H, ArH) ppm; ^{13}C NMR (125 MHz, CD_3CN): δ = 15.6 (CH_3), 56.1 (OCH_3), 57.1 (NCH_2), 66.0 (C-6), 66.2 (OCH_2Ph), 66.9 (C-4), 68.9 (C-2), 75.9 (C-5), 86.6 (C-3), 87.4 (CPh_3), 101.8 (C-1), 127.4–145.2 (Ph) ppm; *m*/*z* (ESI+ve): 612 ($[M+H]^+$, 100%); HRMS *m*/*z* (ESI+ve): found 612.3094 ($[M+H]^+$); $C_{41}H_{42}NO_4$ requires 612.3108.

4.14. 1,5,6-Tri-*O*-acetyl-*N*-benzyl-3-*O*-benzyl-2,4-dideoxy-2,4-imino-3-methyl-D-talitol 26

Compound **25** (135 mg, 0.22 mmol) was dissolved in 1:1 v/v 1,4-dioxane/2 M hydrochloric acid (14 mL) and stirred at 50 °C. After 20 h, the reaction mixture was cooled at rt, diluted with dichloromethane (30 mL), and washed with saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with dichloromethane (2 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude lactol as a yellow oil. This material was re-dissolved in methanol (5 mL), sodium borohydride (11 mg, 0.29 mmol) added and the mixture stirred at rt. After 16 h, mass spectrometry showed no remaining starting material and the formation of a single product (*m*/*z* 358). The mixture was quenched with glacial acetic acid and concentrated in vacuo to afford the crude triol as a white solid. This was re-dissolved in 1:1 pyridine/acetic anhydride (4 mL) and stirred at rt. After 16 h, the mixture was concentrated in vacuo, co-evaporated with toluene (3 × 10 mL), and the residue purified by flash column chromatography on silica gel (10:1 to 1:1, cyclohexane/ethyl acetate) to afford **26** as a colorless oil (86 mg, 81%). $[\alpha]_D^{20} = +38.4$ (*c* 0.31, $CHCl_3$); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3088, 3065, 3031 (Ar), 1744 (OAc); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 3H, CH_3), 1.90, 1.91, 2.01 (s, 3 × 3H, OAc), 3.31 (dd, $J_{2,1}$ = 5.6 Hz, $J_{2,1'}$ = 7.6 Hz, 1H, 2-H), 3.36 (d, $J_{4,5}$ = 9.6 Hz, 1H, 4-H), 3.64 (d, J_{gem} = 13.6 Hz, 1H, NCH_2), 3.74 (dd, $J_{1,1'}$ = 11.6 Hz, $J_{1,2}$ = 5.6 Hz, 1H, 1-H), 3.86 (dd, $J_{1',1}$ = 11.6 Hz, $J_{1',2}$ = 7.6 Hz, 1H, 1′-H), 3.95 (dd, $J_{6,6'}$ = 12.4 Hz, $J_{6,5}$ = 7.2 Hz, 1H, 6-H), 3.98 (d, J_{gem} = 13.6 Hz, 1H, NCH_2), 4.33 (d, J_{gem} = 11.2 Hz, 1H, OCH_2Ph), 4.35 (dd, $J_{6',6}$ = 12.4 Hz, $J_{6',5}$ = 2.8 Hz, 1H, 6′-H), 4.41 (d, J_{gem} = 11.2 Hz, 1H, OCH_2Ph), 5.31–5.34 (m, 1H, 5-H), 7.25–7.37 (m, 5H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (CH_3), 20.9, 21.0 (3 × OAc), 62.0 (NCH_2), 63.6 (C-6 and C-1), 65.3 (OCH_2Ph), 69.8 (C-2), 70.0 (C-4), 72.2 (C-5), 128–138.4 (Ph), 170.4, 170.5, 170.9 (3 × OAc) ppm; *m*/*z* (ESI+ve): 484 ($[M+H]^+$, 100%; 506 ($[M+Na]^+$, 19%); HRMS *m*/*z* (ESI+ve): found 506.2129 ($[M+Na]^+$); $C_{27}H_{33}NNaO_7$ requires 506.2149.

4.15. Methyl *N*-benzyl-3-*O*-benzyl-2,4-dideoxy-2,4-imino-3-methyl-D-ribonate 27

Sodium methoxide (4 mg, 0.07 mmol) was added to a stirred solution of triacetate **26** (86 mg, 0.18 mmol) in methanol (4 mL) at 40 °C. After 18 h TLC analysis (1:1 cyclohexane/ethyl acetate) showed the formation of a single product (R_f 0.00). The mixture was concentrated in vacuo to afford the corresponding triol as a colorless oil (68 mg, quant). Sodium periodate (47 mg, 0.22 mmol) was added to a solution of the triol (60 mg, 0.17 mmol) in water (2 mL) and 1,4-dioxane (0.6 mL), and cooled at 0 °C. After 50 min at 0 °C, TLC analysis (ethyl acetate) showed the formation of a single product (R_f 0.70). Ethanol (10 mL) was added, the reaction stirred for 15 min and the resultant precipitate was removed via filtration (GF/A glass microfibre). The filtrate was concentrated in vacuo at 20 °C to yield an unstable lactol, which was used without any further purification. This was re-dissolved in anhydrous methanol (2 mL) containing potassium carbonate (70 mg, 0.50 mmol). A solution of iodine (55 mg, 0.22 mmol) in methanol (2 mL) was added dropwise and the resulting suspension was stirred at 0 °C under a nitrogen atmosphere. After 2 h, the reaction was quenched with satd aq. sodium thiosulfate and then extracted with ethyl acetate (4 × 7 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo, and the residue purified by flash column chromatography on silica gel (5:1 to 1:2, cyclohexane/ethyl acetate) to afford **27** as a colorless oil (40 mg, 67% from **26**). $[\alpha]_D^{20} = +28.6$ (*c* 0.40, $CHCl_3$); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3088, 3063, 3030 (Ar), 1743 (CO), 1497, 1454 (Ar); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 3H, CH_3), 3.32–3.36 (m, 2H, 4-H and 5-H), 3.47 (d, $J_{5',4}$ = 9.0 Hz, 1H, 5′-H), 3.71 (s, 3H, OCH_3), 3.74 (d, J_{gem} = 12.5 Hz, 1H, NCH_2), 3.88 (s, 1H, 2-H), 3.92 (d, J_{gem} = 12.5 Hz, 1H, NCH_2), 4.49 (d, J_{gem} = 11.0 Hz, 1H, OCH_2Ph), 4.57 (d, J_{gem} = 11.0 Hz, 1H, OCH_2Ph), 7.24–7.37 (m, 5H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8 (CH_3), 51.9 (OCH_3), 59.9 (C-5), 60.8 (NCH_2), 65.5 (OCH_2Ph), 72.0 (C-4), 72.4 (C-2), 78.7 (C-3), 127.6–138.3 (Ph), 170.8 (C-1) ppm; *m*/*z* (ESI+ve): 356 ($[M+H]^+$, 100%; 378 ($[M+Na]^+$, 12%); HRMS *m*/*z* (ESI+ve): found 378.1664 ($[M+Na]^+$); $C_{21}H_{25}NNaO_4$ requires 378.1676.

4.16. *N*-Benzyl-3-*O*-benzyl-2,4-dideoxy-2,4-imino-3-methyl-D-ribonic acid 28

At first, K_2CO_3 (27 mg, 0.20 mmol) was added to a solution of **27** (35 mg, 0.10 mmol) in water (3 mL) and 1,4-dioxane (2 mL). The resulting mixture was stirred at 65 °C. After 72 h, mass spectrometry showed no remaining starting material and the formation of a single product (*m*/*z* 342). The solvents were removed in vacuo and the remaining residue was loaded onto a Serdolit CG-400 I strongly basic ion exchange resin. The column was flushed with water and then eluted with 2 M acetic acid. The acidic fraction was reduced in vacuo to afford **28** as a white solid (32 mg, 95%). Mp 158–160 °C; $[\alpha]_D^{20} = -6.4$ (*c* 0.53, methanol); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 1729 (CO); ^1H NMR (500 MHz, C_5D_5N): δ = 1.88 (s, 3H, CH_3), 3.77–3.82 (m, 2H, 5-H and 4-H), 3.91–3.95 (m, 1H, 5′-H), 3.98 (d, J_{gem} = 13.0 Hz, 1H, NCH_2), 4.24–4.26 (m, 2H, 2-H and NCH_2), 4.96 (s, 2H, OCH_2Ph), 7.26–7.58 (m, 5H, ArH) ppm; ^{13}C NMR (125 MHz, C_5D_5N): δ = 16.0 (CH_3), 62.1 (NCH_2), 62.2 (C-5), 67.0 (OCH_2Ph), 73.9, 74.1 (C-2 and C-4), 80.3 (C-3), 128.5–140.7 (Ph), 173.9 (C-1) ppm; *m*/*z* (ESI+ve): 342 ($[M+H]^+$, 100%; 364 ($[M+Na]^+$, 13%); HRMS *m*/*z* (ESI+ve): found 364.1521 ($[M+Na]^+$); $C_{20}H_{23}NNaO_4$ requires 364.1519.

4.17. 2,4-Dideoxy-2,4-imino-3-methyl-D-ribonic acid 15

At first, 10% Pd on carbon (8 mg) was added to a degassed solution of **28** (19 mg, 0.06 mmol) in 1,4-dioxane (2 mL) and aqueous HCl (2 m, 2 mL) and the resulting solution was stirred at room temperature under hydrogen. After 14 h, the reaction mixture was filtered (GF/A glass microfibre) and the solvents were removed in vacuo to afford **15** as a colorless oil (11 mg, quant). $[\alpha]_D^{20} = +8.4$ (*c* 0.50, methanol); $\widetilde{V}_{max}$ (thin film, cm^{-1}): 3345 (OH), 1732 (CO); ^1H NMR (500 MHz, D_2O): δ = 1.45 (s, 3H, CH_3), 3.95 (d, $J_{5,4}$ = 6.5 Hz, 2H, 5-H), 4.41 (t, $J_{4,5} = J_{4,5'}$ = 6.5 Hz, 1H, 4-H), 4.85 (s, 1H, 2-H) ppm; ^{13}C NMR (125 MHz, D_2O): δ = 16.7 (CH_3), 57.3 (C-

5), 68.5 (C-2), 69.2 (C-4), 74.3 (C-3), 169.0 (C-1) ppm; *m/z* (ESI+ve): 162 ([M+H]$^+$, 100%; HRMS *m/z* (ESI+ve): found 184.0589 ([M+Na]$^+$); $C_6H_{11}NNaO_4$ requires 184.0580.

4.18. Methyl *N*-butyl-2,3,4-trideoxy-2,4-imino-3-methyloxycarbonylmethyl-6-*O*-trityl-β-D-idopyranoside 30

At first, $Bu_3PCH_2CO_2MeBr$ (33 mg, 0.09 mmol) was dissolved in dichloromethane (5 mL) and washed with sodium hydroxide (1 M aq, 5 mL) for 15 min. The aqueous layer was then washed with dichloromethane (2 × 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting ylide was added to a solution of **14** (36 mg, 0.08 mmol) in dichloromethane (2 mL) and the reaction mixture stirred at room temperature for 17 h. After this time, TLC analysis (5:1 toluene/acetone) showed the complete consumption of the starting material (R_f 0.83) and the formation of a major product (R_f 0.68). The solvent was removed in vacuo to afford **29** as a 1:1 mixture of alkenes. This crude was re-dissolved in 1,4-dioxane (1 mL) and 10% Pd on carbon (8 mg) was added. The mixture was degassed and stirred at room temperature under hydrogen. After 16 h, the reaction mixture was filtered (GF/A glass microfibre), the solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (6:1 cyclohexane/ethyl acetate) to afford **30** as a pale yellow oil (21 mg, 51% over two steps). $[\alpha]_D^{20} = -32.4$ (*c* 0.53, $CHCl_3$); $\tilde{V}_{max}$ (thin film, cm^{-1}): 3088, 3058, 3024 (Ar), 1736 (CO); ^{1}H NMR (500 MHz, C_6D_6): δ = 0.96 (t, *J* = 7.3 Hz, 3H, CH_3), 1.33–1.48 (m, 4H, 2 × CH_2), 2.44 (dd, *J* = 7.5 Hz, *J* = 16.0 Hz, 1H, C*H*$_2$CO$_2$), 2.53 (dd, *J* = 8.0 Hz, *J* = 16.0 Hz, 1H, C*H*$_2$CO$_2$), 2.67–2.72 (m, 1H, NC*H*$_2$), 2.79–2.84 (m, 1H, NC*H*$_2$), 3.28–3.31 (m, 1H, 2-H), 3.37 (s, 3H, OCH_3), 3.43 (m, 4H, 4-H and OCH_3), 3.50–3.55 (m, 1H, 3-H), 3.83 (dd, $J_{6,6'}$ = 8.5 Hz, $J_{6,5}$ = 7.5 Hz, 1H, 6-H), 3.92 (dd, $J_{6',6}$ = 8.5 Hz, $J_{6',5}$ = 5.5 Hz, 1H, 6′-H), 4.17–4.20 (m, 1H, 5-H), 4.73 (s, 1H, 1-H), 7.13–7.71 (m, 15H, ArH) ppm; ^{13}C NMR (125 MHz, C_6D_6): δ = 14.4 (CH_3), 20.7 (CH_2), 30.7 (*C*H$_2$CO$_2$), 31.4 (CH_2), 36.0 (C-3), 51.2 (OCH_3), 51.6 (NC*H*$_2$), 55.2 (OCH_3), 63.3 (C-4), 64.9 (C-6), 65.1 (C-2), 73.9 (C-5), 87.0 (*C*Ph$_3$), 99.1 (C-1), 127.2–147.9 (Ph), 172.2 (CO) ppm; *m/z* (ESI+ve): 530 ([M+H]$^+$, 100%); HRMS *m/z* (ESI+ve): found 530.2886 ([M+H]$^+$); $C_{33}H_{40}NO_5$ requires 530.2901.

4.19. Methyl *N*-butyl-2,4-dideoxy-2,4-imino-3-*O*-trifluoromethanesulfonyl-6-*O*-trityl-β-D-talopyranoside 32

Trifluoromethanesulfonic anhydride (0.01 mL, 0.06 mmol) was added to a stirred solution of alcohol **12** (20 mg, 0.04 mmol) and pyridine (0.01 mL, 0.13 mmol) in dichloromethane (1 mL) at −30 °C under a nitrogen atmosphere. TLC analysis (1:1 cyclohexane/ethyl acetate) after 1 h indicated no starting material (R_f 0.14) and the formation of a single product (R_f 0.91). The mixture was diluted with dichloromethane (5 mL), washed with saturated aqueous $CuSO_4$ (5 mL), and the organic layer dried ($MgSO_4$), filtered, and concentrated in vacuo at 25 °C. The residue was purified by flash column chromatography on silica gel (3:1 cyclohexane/ethyl acetate) to afford **32** as a colorless oil (24 mg, 95%). $[\alpha]_D^{20} = -27.1$ (*c* 0.41, CH_2Cl_2); $\tilde{V}_{max}$ (thin film, cm^{-1}): 3087, 3060, 3025, 1491, 1449 (Ar); ^{1}H NMR (500 MHz, C_6D_6): δ = 0.78 (t, *J* = 9.0 Hz, 3H, CH_3), 1.12–1.28 (m, 4H, 2 × CH_2), 2.56–2.62 (m, 1H, NC*H*$_2$), 2.88–2.94 (m, 1H, NC*H*$_2$), 3.12 (s, 3H, OCH_3), 3.27 (dd, $J_{6,6'}$ = 11.0 Hz, $J_{6,5}$ = 8.5 Hz, 1H, 6-H), 3.43 (d, $J_{2,4}$ = 6.5 Hz, 1H, 2-H), 3.61 (d, $J_{4,2}$ = 6.5 Hz, 1H, 4-H), 3.69 (dd, $J_{6',6}$ = 11.0 Hz, $J_{6',5}$ = 8.0 Hz, 1H, 6′-H), 3.76 (t, $J_{5,6}$ = = $J_{5,6'}$ = 8.0 Hz, 1H, 5-H), 4.18 (s, 1H, 1-H), 4.58 (s, 1H, 3-H), 7.00–7.53 (m, 15H, ArH) ppm; ^{13}C NMR (125 MHz, C_6D_6): δ = 14.2 (CH_3), 20.5 (CH_2), 30.5 (CH_2), 49.1 (NC*H*$_2$), 56.2 (OCH_3), 64.9 (C-6), 66.1 (C-4), 67.8 (C-2), 73.8 (C-5), 87.2 (*C*Ph$_3$), 89.5 (C-3), 99.7 (C-1), 127.8–144.3 (Ph) ppm; *m/z* (ESI+ve): 606 ([M+H]$^+$, 60%), 628 ([M+Na]$^+$, 15%); HRMS *m/z* (ESI+ve): found 628.1944 ([M+Na]$^+$); $C_{31}H_{34}F_3NNaO_6S$ requires 628.1951.

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