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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of 1,4-dideoxy-1,4-imino-D-ribitol via stereoselective addition of allylphenylsulfone to an aryl *N*-sulfinylimine†

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Abstract—Asymmetric synthesis of 1,4-dideoxy-1,4-imino-D-ribitol was achieved utilizing the stereoselective addition of allylphenylsulfone to a chiral *N*-sulfinyl-2-furfuryl imine and ring-closing metathesis reactions as key steps. © 2002 Published by Elsevier Science Ltd.

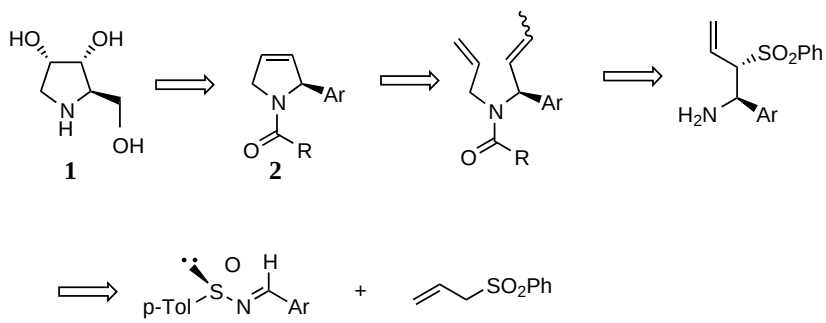
1. Introduction

The core structure of an azasugar may contain various heterocyclic ring systems such as polyhydroxy-pyrrolidines, piperidines or indolizidines. Because of their ability to mimic carbohydrates in various biological processes, azasugars are found to have activities against cancer, diabetes and viral infections.[2] There have been a number of synthetic efforts to reach these targets both from carbohydrate[3] and non-carbohydrate starting materials,[4] but many of these routes suffer from excessive length and/or lack of selectivity. It is to be noted that asymmetric routes to azasugars require the incorporation of three or four stereogenic centers consisting of three to four hydroxyl substituents.

Retrosynthetic analysis (Scheme 1) shows that non-racemic (2*S*)-2-aryl-3-pyrrolines of the type **2** would offer a highly versatile entry into azasugar **1**. Since pyrroline **2** possesses fixed stereochemistry at C(2), we envisaged that stereoselective dihydroxylation followed by oxidative cleavage of the 2-aryl ring and functional group manipulations should provide the targeted structure **1**. We herein describe the synthesis of *N*-Boc-(2*S*)-2-furyl-3-pyrroline **2a**, following a modification of our earlier procedure[5] (using BOC protection in this case) and its further elaboration to azasugar **1**.

2. Results and discussion

Our synthesis commenced with the stereoselective addition of lithiated allylphenylsulfone carbanion not bearing any additional functions, to non-racemic sulfinylimine **3**[6] (Eq. (1)). Allylphenylsulfone was deprotonated



Scheme 1.

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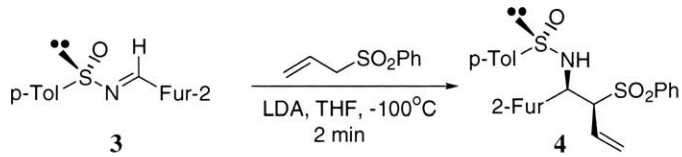
with lithium diisopropylamide (LDA) in THF at −100°C, followed by the addition of the sulfinylimine **3** in THF. The reaction was complete within 2 min to afford **4** as a 1:2 mixture of two diastereomers, which were not separable by column chromatography. Varying the reaction conditions did not improve the diastereoselectivity. The diastereomeric ratio was determined by integration of the α-sulfonyl proton of both isomers in the ^{1}H NMR spectrum. In the major isomer the proton appeared as a dd (J=9.9, 2.7 Hz) and in the minor isomer as a dd with J=9.9, 3.3 Hz.



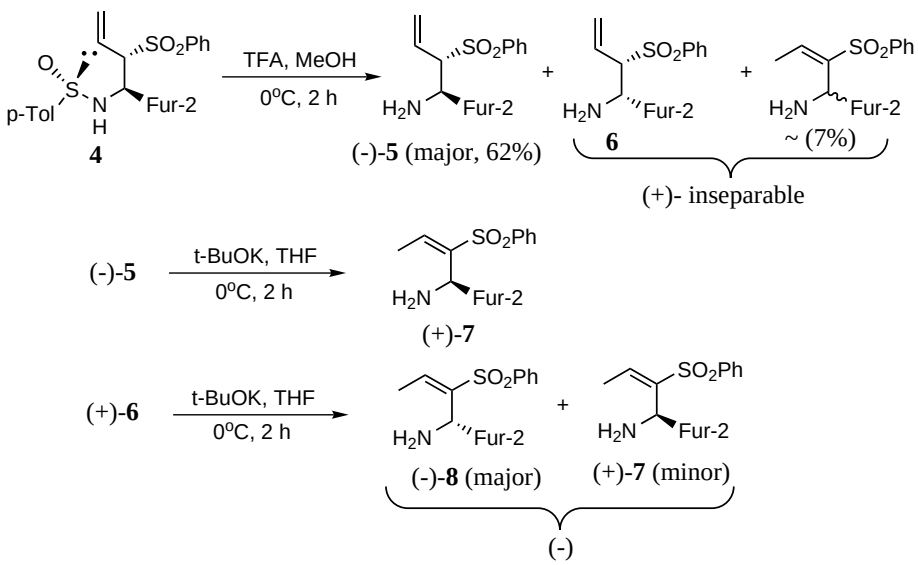
3 **4** (1)

1:2 mixture of diastereomers

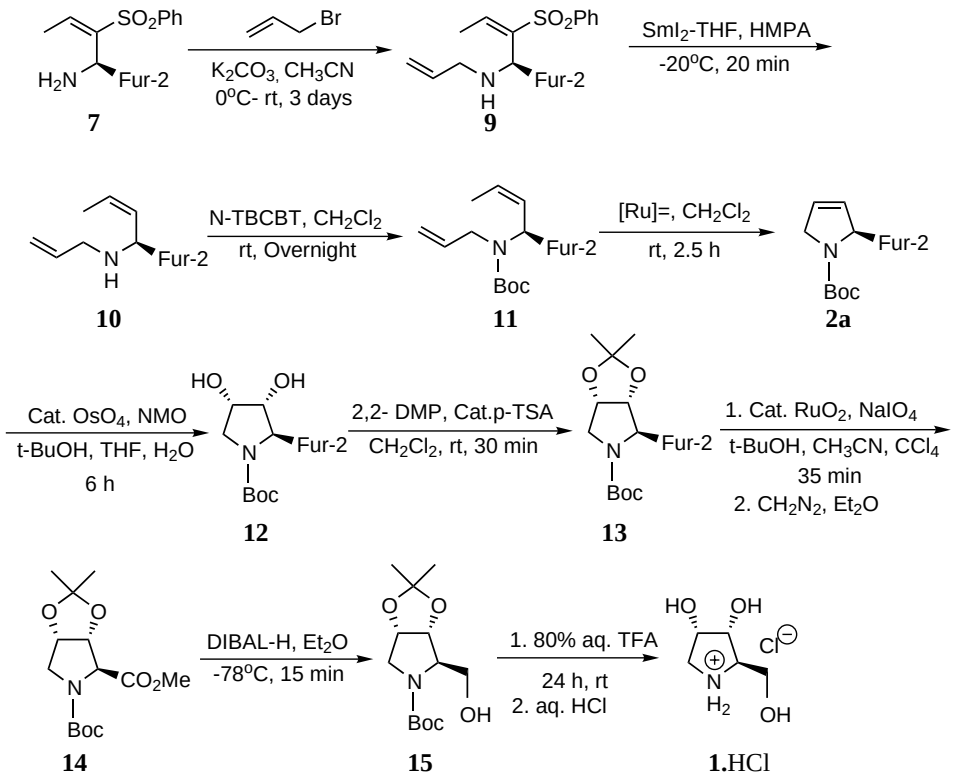
Removal of the sulfonyl group in **4** by treatment with TFA afforded chromatographically separable diastereomers **5** and **6** (Scheme 2) with the diastereomeric ratio elucidated as above for the isomers of **4**. In order to determine the absolute configuration at the carbon α to the amino function, we intended to isomerize the double bond in **5** and **6** independently. Exposure of **5** and **6**, respectively, to a catalytic amount of *tert*-BuOK afforded **7** and **8**, whose specific rotations (+31 and −13), though of opposite direction, were not of the same magnitude, confirming primarily the fact that they are indeed epimers with respect to C(4). Careful analysis of the ^{1}H NMR spectrum of **6** indicated that it was contaminated with nearly 7% of isomerized products **7** and/or **8**. Presumably the major contaminant was **7** (derived from the major product **5** as indicated by the reduced negative rotation of **8** compared to (+)-**7**). The isomerization during sulfone addition could not be avoided by reducing the amount of base or by adding Lewis acids as reported in some examples in the literature.[7]

With **5** and **7** in hand, our next goal was to convert them to **1**. Monoallylation of **7** using allyl bromide in the presence of K_2CO_3 gave **9** (Scheme 3). Further, reductive removal of the sulfonyl group with SmI_2 to produce **10** followed by Boc protection of the amine function set the stage for a metathesis ring closure to obtain the targeted pyrroline ring. Treatment of **11** with 5 mol% of Grubbs catalyst[8] [$Cl_2(Pcy_3)_2Ru$=CHPh] in CH_2Cl_2 at room temperature afforded pure pyrroline **2a** as a mixture of two carbamate rotamers.

Dihydroxylation on **2a** under standard reaction conditions using a catalytic amount of OsO_4 in conjunction with NMO (*N*-methylmorpholine oxide) in a three solvent system afforded **12** as a single isomer (Scheme 3). The observed selectivity can be explained by the presence of the β-oriented C_2-furyl group which allows the osmylation to take place only from the α-face purely on steric grounds. Protection of the diol as its isopropylidine derivative gave the expected **13**. The assigned structure was deduced from 2D COSY, NOESY and HMQC experimental data. Having incorporated the vicinal hydroxyl groups in a stereoselective manner at positions C(3) and C(4), our attention was directed towards converting the 2-furyl group at C(2) into a hydroxymethyl function. In our hands, oxidation of the furyl ring using a catalytic amount of $RuCl_3{\times}H_2O$[9] and



Scheme 2.



Scheme 3.

5 equiv. of $NaIO_4$ followed by treatment with diazomethane gave **14** in only poor yield. On the other hand, oxidation using a catalytic amount of $RuO_2 \times H_2O$[10] and 5 equiv. of $NaIO_4$ followed by esterification using diazomethane improved the yield of **14** to 82%. Reduction of the ester using 5 equiv. of DIBAL-H in ether at −78°C gave the alcohol **15** in high yield. Stirring **15** at room temperature in 80% aq. TFA for 24 h then effected global deprotection to afford our target compound **1** as the trifluoroacetate salt. Treatment of this trifluoroacetate salt with aq. NaOH followed by chromatographic purification on Dowex-H^+ afforded the free base **1**, which was converted (vide Section 2) into **1**·HCl. The specific rotation of **1**·HCl in comparison with the literature value[3d] indicated it to be 94% enantiomerically pure. Since the dihydroxylation of **2a** had proceeded with near 100% stereoselectivity, we attribute the presence of 3% of enantiomer due either to minor contamination of **2a** with its enantiomer or partial racemization in one of the synthetic steps.

3. Experimental

3.1. General

All air- and moisture-sensitive reactions were carried out in flame-dried, argon-flushed, two-necked flasks sealed with rubber septa, and the dry solvents and reagents were introduced with a syringe. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Reactions with cooling at −100°C were performed using a mixture of liquid nitrogen and MeOH. Flash column chromatography was done on Merck silica gel 60 (230–400 mesh), and pre-coated Merck silica gel plates (60F-25H) were used for TLC. Unless otherwise mentioned ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer. COSY, NOESY and HMQC spectra were recorded on a Bruker AM-600 spectrometer. Coupling constants were determined directly from ^1H NMR spectra. Mass spectra (CI) were recorded at 60–70 eV. Optical rotations were measured on a Perkin–Elmer 141 polarimeter with path length of 0.1 dm. Chiral sulfinylimine **3** was prepared following the Davis procedure.[6]

3.2. Preparation of (+)-(S_s,3*S*,4*R*)-3-phenylsulfonyl-4-(2-furyl)-4-[*N*-(*p*-tolylsulfinyl) amino]-but-1-ene 4

In a two-necked, round-bottomed flask equipped with an argon inlet, rubber septum and a stirring bar was placed diisopropylamine (0.36 mL, 2.64 mmol) in THF (4 mL). At −50°C, *n*-BuLi (1.6 M in hexane, 1.5 mL, 2.4 mmol) was added dropwise and stirred for 15 min at the same temperature. The flask was further cooled to −100°C and a solution of allylphenylsulfone (436 mg, 2.4 mmol) in THF (10 mL) was added dropwise. After 20 min a solution of sulfinylimine **3** (466 mg, 2 mmol) in THF (5 mL) was added dropwise along the sides of the flask and after 2 min, TLC analysis indicated consumption of the starting material. The reaction was quenched by adding saturated aq. NH_4Cl (1 mL) and extracted thoroughly with dichloromethane (3×30 mL). The combined organic extract was washed with brine,

dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (40% EtOAc in hexane) yielded **4** (795 mg, 96%) as an inseparable mixture of two diastereomers in a 1:2 ratio: mp 70°C; $[\alpha]_D^{25}$ +79 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) For the major diastereomer δ 7.86 (tt, 2H, $J=7$,1.2 Hz), 7.69 (d, 2H, $J=8.1$ Hz), 7.63 (tt, 1H, $J=6.9$, 2.7 Hz), 7.54 (tt, 2H, $J=6.6$, 1.2 Hz), 7.35 (dd, 1H, $J=4$, 1.8 Hz), 7.28 (d, 2H, $J=8.1$ Hz), 6.46 (d, 1H, exchangeable with D_2O, $J=3.3$ Hz), 6.36 (dd, 1H, $J=2.7$, 1.2 Hz), 6.27 (dd, 1H, $J=3.3$, 1.8 Hz), 5.92 (dt, 1H, $J=17.1$, 9.9 Hz), 5.46, (br d, 1H, $J=3$ Hz), 5.29 (dd, 1H, $J=10.8$, 1.5 Hz), 4.95 (d, 1H, $J=17.1$ Hz), 4.24 (dd, α-sulfonyl proton from the major isomer, $J=9.9$, 2.7 Hz), 4.04 (dd, α-sulfonyl proton from the minor isomer, $J=9.9$, 3.3 Hz) 2:1 ratio, 2.4 (s, 3H). ^{13}C NMR δ 151.43, 150.22, 142.74, 141.7, 134.19, 130.06, 129.89, 129.56, 127.03, 126.45, 125.8, 125.66, 110.9, 109.32, 73, 53.05, 21.74.

3.3. (−)-(3*S*,4*R*)-4-Amino-3-phenylsulfonyl-4(2-furyl)but-1-ene 5

Into a single-necked, round-bottomed flask equipped with a stirring bar and a rubber septum was placed **4** (794 mg, 1.9 mmol) in MeOH (10 mL) at 0°C under an Ar atmosphere. Trifluoroacetic acid (0.5 mL, 6.43 mmol) was added dropwise and the resultant solution was stirred at the same temperature for 2 h until complete disappearance of the starting material. The reaction mixture was then concentrated and the residual oil was dissolved in CH_2Cl_2 and transferred into a beaker. The beaker was immersed in an ice bath and a satd aq. $NaHCO_3$ was added until the pH rose to 8. The contents of the beaker were transferred into a separatory funnel and the mixture was extracted with CH_2Cl_2 (3×25 mL). The combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated. Purification of the crude product by flash column chromatography (45% EtOAc in hexane) afforded the major isomer **5** as a viscous oil (348 mg, 66%). The minor isomer **6** (166 mg) obtained upon elution with the same solvent system was found to be contaminated with a minor amount of the isomerized product. This impure isomer was not further studied. The major isomer **5** showed $[\alpha]_D^{25}$ −32 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.88 (dd, 2H, $J=8.7$, 0.72 Hz), 7.64 (tt, 1H, $J=7.5$, 2 Hz), 7.53 (tt, 2H, $J=7.5$, 2 Hz), 7.28 (dd, 1H, $J=5.8$, 0.6 Hz), 6.28 (dd, 1H, $J=3$, 1.5 Hz), 6.24 (dd, 1H, $J=5.8$, 3 Hz), 6.05 (dt, 1H, $J=17.1$, 10.2 Hz), 5.28 (dd, 1H, $J=9$, 3 Hz), 5.06 (d, 1H, $J=2.1$ Hz), 4.8 (dd, 1H, $J=17.1$, 3 Hz), 3.93 (dd, 1H, $J=9$, 3 Hz), 2.03 (br s, 2H, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) δ 154.25, 141.8, 137.67, 133.82, 129.3, 128.91, 125.59, 125.45, 110.3, 106.6, 72.52, 48.92. HRMS observed mass = 278.084419 (for MH^+ calculated mass = 278.085090).

3.4. (+)-(4*R*)-4-Amino-3-phenylsulfonyl-4(2-furyl)-2(*E*)-butene 7

To a stirred solution of amine **5** (316 mg, 1.14 mmol) in THF (6 mL) at 0°C under an Ar atmosphere was added *tert*-BuOK (5 mg) in one portion and the resultant mixture was stirred at the same temperature for 2 h, when complete disappearance of **5** with appearance of a polar spot on TLC was observed. Cold water (1 mL) was added to quench the reaction and the mixture was extracted thoroughly with CH_2Cl_2 (3×20 mL). The combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude mass by flash column chromatography (50% EtOAc in hexane) afforded **7** as a pale yellowish oil (284 mg, 90%): $[\alpha]_D^{25}$ +31 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.71 (dd, 2H, $J=7.5$, 3 Hz), 7.52 (tt, 1H, $J=7.5$, 3 Hz), 7.44 (tt, 2H, $J=7.5$, 3 Hz), 7.24 (q, 1H, $J=7.3$ Hz), 7.0 (br s, 1H), 6.18 (br d, 2H, $J=2$ Hz), 5.14 (br s, 1H), 2.57 (br s, 2H, exchangeable with D_2O), 1.95 (d, 3H, $J=7.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 154.11, 143.58, 142.13, 141.78, 140.56, 133.22, 129.29, 128.07, 110.69, 106.91, 48.14, 14.71. HRMS observed mass = 278.082072 (for MH^+ calculated mass = 278.085090).

3.5. (−)-(4*R*)-*N*-(2-Propenyl)-3-phenylsulfonyl-4-(2-furyl)-2(*E*)-butenyl amine 9

In a single-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed K_2CO_3 (455 mg, 3.3 mmol) in CH_3CN (2 mL) at 0°C under an Ar atmosphere. Solutions of amine **7** (457 mg, 1.65 mmol) in CH_3CN (4 mL) and allyl bromide (240 mg, 1.98 mmol) in CH_3CN (1 mL) were added successively. The reaction mixture was brought to room temperature and stirred for 3 days, when complete disappearance of **7** with appearance of a non-polar spot on TLC was observed. Cold water (1 mL) was added to quench the reaction and the mixture was extracted thoroughly with CH_2Cl_2 (3×20 mL). The combined organic extract was then washed with brine, dried ($MgSO_4$) and concentrated. Purification of the crude product by flash column chromatography (14% EtOAc) afforded pure **9** (408 mg, 78%): $[\alpha]_D^{25}$ −13 (*c* 2.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.67 (dt, 2H, $J=8.4$, 3 Hz), 7.5 (tt, 1H, $J=7.5$, 3 Hz), 7.4 (tt, 2H, $J=7.5$, 3 Hz), 7.26 (q, 1H, $J=7$ Hz), 6.98 (dd, 1H, $J=6$, 2 Hz), 6.1 (dd, 1H, $J=6$, 2 Hz), 6.08 (dd, 1H, $J=6$, 2 Hz), 5.8 (ddt, 1H, $J=17.1$, 10.5, 5.7 Hz), 5.15 (ddt, 1H, $J=17.1$, 2, 0.6 Hz), 5.07 (dq, 1H, $J=10.5$, 2 Hz), 4.88 (s, 1H), 3.17 (dddt, 2H, $J=17$, 12.2, 6, 1.5 Hz), 2.19 (br s, 1H, exchangeable with D_2O), 2.02 (d, 3H, $J=7$ Hz); ^{13}C NMR ($CDCl_3$) δ 151.95, 142.21, 141.22, 140.39, 139.9, 135.65, 132.25, 128.32, 127.32, 116.09, 109.77, 106.79, 52.7, 49.2, 14.22. HRMS observed mass = 317.107283 (for MH^+ calculated mass = 317.108565).

3.6. (+)-(4*S*)-*N*-(2-Propenyl)-4-(2-furyl)-2(*Z*)-butenyl amine 10

To a stirred solution of **9** (180 mg, 0.57 mmol) in SmI_2–THF solution (0.1 M, 22.5 mL) at −20°C under Ar atmosphere was added HMPA (2 mL) dropwise. The resulting mixture was stirred at the same temperature for 20 min and then quenched with aq. NH_4Cl (1 mL). THF was removed under reduced pressure and extracted with EtOAc (3×25 mL). The combined organic extract was washed with brine, dried ($MgSO_4$)

and concentrated. Purification of the crude by flash column chromatography (15% EtOAc in hexane) afforded pure **10** (60 mg, 59%) as an oil: $[\alpha]_D^{25}$ +22.6 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.35 (dd, 1H, $J=1.8$, 0.6 Hz), 6.3 (dd, 1H, $J=3$, 1.8 Hz), 6.17 (dt, 1H, $J=3$, 1 Hz), 5.92 (ddt, 1H, $J=17.4$, 10, 6 Hz), 5.69 (dqd, 1H, $J=10.8$, 6.6, 1.2 Hz), 5.55 (tq, 1H, $J=10.8$, 1.8 Hz), 5.18 (dq, 1H, $J=17.4$, 1.8 Hz), 5.11 (dq, 1H, $J=10.8$, 1.8 Hz), 4.67 (d, 1H, 10.8 Hz), 3.24 (qdt, 2H, $J=18$, 6, 1.4 Hz), 1.7 (dd, 3H, $J=6.6$, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 156.04, 142.09, 136.87, 130.04, 127.53, 116.74, 110.4, 106.22, 52.31, 49.94, 13.65. HRMS observed mass = 177.118442 (for M^+ calculated mass = 177.115364).

3.7. (−)-(4*S*)-*N*-Boc-*N*-(2-propenyl)-4-(2-furyl)-2(*Z*)-butenyl amine 11

In a single-necked flask equipped with a rubber septum and an argon inlet was placed freshly prepared *tert*-butoxycarbonyloxybenzotriazole[11] (282 mg, 1.2 mmol) under an Ar atmosphere at room temperature. A CH_2Cl_2 (3 mL) solution of **10** (177 mg, 1 mmol) was added dropwise and the mixture was stirred overnight. Removal of the solvent under reduced pressure followed by chromatographic purification (11% EtOAc in hexane) afforded **11** (221 mg, 80%) as a mixture of two rotamers: $[\alpha]_D^{25}$ −25 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.34 (m, 1H), 6.29 (m, 1H), 6.17 (m, 1H), 5.62–5.8 (m, 4H), 4.96 (m, 2H), 1.7 and 1.75 (2d, 3H, $J=7$ Hz), 1.46 and 1.45 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ (carbonyl peak was not seen due to line broadening)155.24 and 153.72, 141.8, 135.23, 129.31 and 128.88, 126.6 and 125.83, 115.38, 110.1, 107.87 and 107.6, 79.87, 54.99 and 50.1, 46.96, 28.4, 17.83 and 13.45. HRMS observed mass = 278.173345 (for MH^+ calculated mass = 278.175619).

3.8. (−)-(2*S*)-*N*-Boc-2-(2-furyl)-3,4-dehydropyrrolidine 2a

In a two-necked flask equipped with a magnetic stirring bar, rubber septum and an argon inlet was placed Grubbs catalyst (25 mg, 0.03 mmol) under an Ar atmosphere. A solution of **11** (167 mg, 0.6 mmol) in CH_2Cl_2 (2 mL) was introduced by syringe and the resultant pink colored solution was stirred for 2.5 h when TLC analysis indicated the total disappearance of **11**. The reaction mixture was exposed to air and concentrated. Purification of the crude product by flash column chromatography (10% EtOAc in hexane) afforded pure **2a** (130 mg, 92%) as a mixture of two rotamers: $[\alpha]_D^{25}$ −101.8 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35–7.29 (m, 1H), 6.32–6.14 (m, 2H), 5.97–5.91 (m, 1H), 5.74–5.72 (m, 1H), 5.6 and 5.49 (2 br, 1H), 4.26–4.22 (m, 2H), 1.45 and 1.35 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 174, 154.24 and 153.99, 141.71 and 141.41, 127.75, 126.45, 110.24, 106.81 and 106.31, 79.68, 61.16 and 60.98, 53.41 and 52.95, 28.46 and 28.26. HRMS observed mass = 235.120955 (for M^+ calculated mass = 235.120844).

3.9. (−)-(2*R*,3*R*,4*S*)-*N*-Boc-2-(2-furyl)pyrrolidine-3,4-diol 12

In a single-necked flask equipped with a magnetic stirring bar and a rubber septum was placed NMO (72 mg, 0.612 mmol) in *t*-BuOH, THF and H_2O (0.6, 0.2, 0.1 mL, respectively) at room temperature under an Ar atmosphere. Osmium(VIII) oxide (3 mg, 0.012 mmol) was then added in one portion. A THF (1 mL) solution of **2a** (155 mg, 0.6 mmol) was added dropwise and the resultant mixture was stirred for 6 h. The reaction mixture was passed through a thick pad of silica gel to remove the colored mass and washed with EtOAc (50 mL). Washing of the filtrate with brine, drying ($MgSO_4$) and evaporation followed by flash column chromatographic purification afforded pure **12** as a colorless solid (148 mg, 92%): mp 75–77°C; $[\alpha]_D^{25}$ −15.7 (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32 (d, 1H, $J=3$ Hz), 6.3 (t, 1H, $J=3$ Hz), 6.18 (br s, 1H), 4.69 and 4.75 (2 br s, 1H), 4.45 (q, 1H, $J=5.7$ Hz), 4.2 (t, 1H, $J=3.6$ Hz), 3.74 (dd, 1H, $J=11.1$, 6 Hz), 3.49 (br s, 1H), 3.17 (br s, 2H, exchangeable with D_2O), 1.4 and 1.3 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ (carbonyl peak was not seen due to line broadening) 154.75, 141.72, 110.32, 107.07, 80.26, 76.78 and 75.53, 70.58 and 69.9, 60.69, 50.4, 28.2. HRMS observed mass = 270.133424 (for MH^+ calculated mass = 270.134148).

3.10. (−)-(2*R*,3*R*,4*S*)-*N*-Boc-2-(2-furyl)-3,4-isopropylidenedioxypyrrolidine 13

In a single-necked flask equipped with an argon inlet, a rubber septum and magnetic stirring bar was placed *p*-TSA (3 mg) under an Ar atmosphere at room temperature. A solution of **12** (85 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) followed by 2,2-dimethoxypropane (0.156 mL, 1.28 mmol) were introduced by syringe. After stirring for 30 min, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (20% EtOAc in hexane) to afford pure **13** (82 mg, 83%) as a mixture of two rotamers: $[\alpha]_D^{25}$ −41.3 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) For the major rotamer δ 7.34 (d, 1H, $J=1.5$ Hz), 6.31 (dd, 1H, $J=3$,1.5 Hz), 6.13 (d, 1H, $J=3$ Hz), 5.02 (br s, 1H), 4.87 (t, 1H, $J=5.5$ Hz), 4.8 (d, 1H, $J=6$ Hz), 3.9 (dd, 1H, $J=13$, 1.5 Hz), 3.58 (dd, 1H, $J=12.5$, 5 Hz), 1.4 (s, 9H), 1.52 and 1.33 (2s, 6H) and for the minor isomer δ 7.34 (d, 1H, $J=1.5$ Hz), 6.31 (dd, 1H, $J=3$,1.5 Hz), 6.2 (d, 1H, $J=3$ Hz), 5.22 (br s, 1H), 4.84 (t, 1H, $J=5.5$ Hz), 4.8 (d, 1H, $J=6$ Hz), 3.88 (d, 1H, $J=13$, 1.5 Hz), 3.53 (dd, 1H, $J=12.5$, 4.5 Hz), 1.46 (s, 9H), 1.5 and 1.3 (2s, 6H); ^{13}C NMR ($CDCl_3$) (carbonyl peak was not seen due to line broadening) δ 154.33, 142.19, 111.91, 110.22, 106.85 and 106.58, 84.16 and 83.54, 80.07 and 79.86, 78.92, 61.22 and 60.74, 52.38 and 51.84, 29.7, 26.87, 24.96. HRMS observed mass = 309.157261 (for M^+ calculated mass = 309.157623).

3.11. (−)-(2*S*,3*R*,4*S*)-*N*-Boc-2-carbomethoxy-3,4-isopropylidinedioxypyrrolidine 14

To a well stirred mixture of CH_3CN (3.2 mL), CCl_4 (2 mL) and H_2O (3.2 mL) were added sequentially $NaIO_4$ (691 mg, 3.25 mmol) and $RuO_2 \cdot H_2O$ (8.6 mg, 0.065 mmol). The mixture was stirred vigorously at room temperature. After 30 min, the resulting mixture was treated with **13** (201 mg, 0.65 mmol) in CH_3CN (2 mL). The solution turned black during 5 min and enough $NaIO_4$ was added in small portions to turn the color to

light green. The mixture was diluted with water and extracted with EtOAc (3×20 mL). The combined organic extract was washed sequentially with 20% aq. $NaHSO_3$ until colorless and then with brine and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude acid was dissolved in Et_2O, cooled to 0°C and treated with an ethereal solution of diazomethane until a slight yellow color persisted. The excess diazomethane was quenched with acetic acid. The resulting solution was concentrated under reduced pressure and the crude ester was purified by flash column chromatography (25% EtOAc in hexane) on silica gel to afford pure **14** (160 mg, 82%): $[\alpha]_D^{25}$ −9.4 (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.74–4.7 (m, 2H), 4.58 (br s, 1H), 4.4 (br s, 1H), 3.83 (dd, 1H, $J=16.2$, 12.6 Hz), 3.76 (s, 3H), 3.57 (td, 1H, $J=12.6$, 4.2 Hz), 1.49, 1.48 and 1.32 (3s, 6H), 1.47 and 1.42 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 199.17, 171.2, 112.54, 83.27 and 82.49, 80.53, 79.57 and 78.6, 66.36 and 65.81, 52.42 and 52.32, 51.96, 28.32 and 28.24, 26.91 and 26.85, 25. HRMS observed mass = 301.150730 (for M^+ calculated mass = 301.152538).

3.12. (2*R*,3*R*,4*S*)-*N*-Boc-2-hydroxymethyl-3,4-isopropylidinedioxypyrrolidine 15

In a two-necked flask equipped with an argon inlet, magnetic stirring bar and a rubber septum was placed ester **14** (135 mg, 0.45 mmol) in Et_2O (6 mL) under an Ar atmosphere at −78°C. DIBAL-H (1 M solution in hexanes, 2.25 mL, 2.25 mmol) was added dropwise and stirred for 15 min. Water (1 mL) was added to quench the reaction. The mixture was diluted with DCM (30 mL) and filtered through a pad of anhydrous $MgSO_4$. The filtrate was dried ($MgSO_4$) and concentrated. Purification of the crude by flash column chromatography (40% EtOAc in hexane) afforded pure **15** (98 mg, 80%) as a mixture of two rotamers: $[\alpha]_D^{25}$ −19.4 (*c* 1.77, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) For the major rotamer δ 4.79 (d, 1H, $J=6$ Hz), 4.78 (dt, 1H, $J=6$, 1.5 Hz), 4.62 (dd, 1H, $J=6$, 1.5 Hz), 4.15 (t, 1H, $J=5$ Hz), 3.79 (dd, 1H, $J=13$, 5 Hz), 3.78 (ddd, 1H, $J=14$, 10, 5 Hz), 3.52 (dd, 1H, $J=13$, 5 Hz), 1.52 (s, 3H), 1.47 (s, 9H), 1.35 (s, 3H); For the minor rotamer δ 4.84 (dt, 1H, $J=6$, 1.5 Hz), 4.79 (d, 1H, $J=6$ Hz), 4.62 (dd, 1H, $J=6$, 1.5 Hz), 4.01 (t, 1H, $J=5$ Hz), 3.81 (br d, 1H, $J=4$ Hz), 3.79 (dd, 1H, $J=13$, 5 Hz), 3.6 (dd, 1H, $J=13$, 6 Hz), 1.52 (s, 3H), 1.48 (s, 9H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) (carbonyl peak was not seen due to line broadening) δ 112, 82.43, 80.68, 79.33, 65.57, 63.81, 53.05, 28.75, 27.43, 25.43. HRMS observed mass = 274.165627 (for MH^+ calculated mass = 274.165448).

3.13. (+)-1,4-Dideoxy-1, 4-imino D-ribitol hydrochloride 1·HCl

The protected ribitol **15** (136.5 mg, 0.5 mmol) was dissolved in 80% aq. trifluoroacetic acid (3 mL) and stirred at room temperature under an Ar atmosphere for 24 h. TLC analysis indicated the absence of starting material. The solvent was removed and the resulting trifluoroacetate salt was neutralized with dilute aq. NaOH and purified by ion exchange chromatography (Dowex 50x, 80–100, H^+ form, eluted with 0.5 M aq. NH_4OH) to give 1,4-dideoxy-1,4-imino-D-ribitol which was dissolved in water (3 mL) and the pH of the solution was adjusted to 4 with dilute aq. HCl to afford, after freeze drying, 1,4-dideoxy-1,4-imino-D-ribitol hydrochloride **1** (64 mg, 75%): mp 130–132°C; $[\alpha]_D^{20}$ +53.9 (*c* 1, H_2O) [lit.[3d] $[\alpha]_D^{20}$ +57.6 (*c* 0.59, H_2O)] ^1H NMR (D_2O, 600 MHz) δ 4.37 (td, C_2H, $J=4.2$, 1.9 Hz), 4.19 (dd, C_3H, $J=8.4$, 4.2 Hz), 3.96 (dd, C_5H, $J=12.6$, 3.4 Hz), 3.82 (dd, $C_{5'}H$, $J=12.6$, 6 Hz), 3.62 (m, C_4H), 3.49 (dd, C_1H, $J=13$, 4.2 Hz), 3.36 (dd, $C_{1'}H$, $J=13$, 2 Hz); ^{13}C NMR (D_2O) δ 50.66, 59.04, 62.84, 70.46, 72.21.

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