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Synthesis of 1,4-dideoxy-1,4-imino-derivatives of D-allitol, L-allitol and D-talitol: a stereo selective approach for azasugars☆

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Abstract—A stereo selective approach for the azasugars 1,4-dideoxy-1,4-imino-D-allitol, L-allitol, and 1,4-dideoxy-1,4-imino-D-talitol is described for different olefin compounds **I** derived from (*R*)-2,3-*O*-isopropylidine glyceraldehyde, L-ascorbic acid, and D-isoascorbic acid by using vinyl Grignard addition, allylation, RCM, and dihydroxylation as the key steps.

1. Introduction

Many pyranoses and furanoses with the ring oxygen replaced by an imino group are natural products and useful as potent glycosidase inhibitors.[1] In recent years these azasugars, both natural and unnatural, have been of intense interest due to their promising chemotherapeutic properties against diabeties, cancer, and viral infections including AIDS.[2]

Among these azasugars 1,4-dideoxy-1,4-imino hexitols (Fig. 1), which belong to a family of polyhydroxylated pyrrolidines are potent glycosidase inhibitors. There are various synthetic approaches to imino sugars, most of them starting from carbohydrate templates. However many of these require a large number of steps, including extensive protecting group manipulations.[3] As a part of our on going program to utilize ring-closing metathesis (RCM) reaction[4] to construct functionalized carbocycles and heterocycles from a diene precursors, we recently communicated[4c] the synthesis of 1,4-dideoxy-1,4-imino-D-allitol **1** and now wish to report a detailed account of our approach and its extension to the synthesis of 1,4-dideoxy-1,4-imino-D-allitol **1**, 1,4-dideoxy-1,4-imino-D-talitol **2**, and the protected form of 1,4-dideoxy-1,4-imino-L-allitol **3**, using allylation, RCM, and dihydroxylation as key steps.

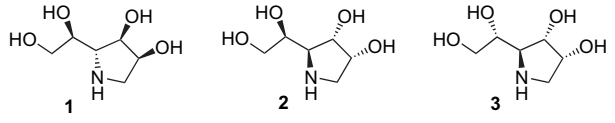
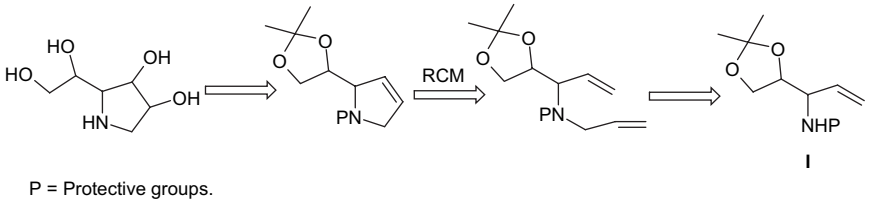


Figure 1.

Our general retrosynthetic analysis of 1,4-dideoxy-1,4-imino hexitols is outlined in Scheme 1, which illustrates the importance of olefin compound **I** and ring-closing metathesis (RCM) in our synthetic endeavors. In turn, the different diastereomers of olefin compound **I** can be prepared from different starting materials.

2. Results and discussions

According to our previous work on the synthesis of cytoxazone[5] compound **6** was prepared through a reaction sequence based on a stereo-controlled addition of vinylmagnesium bromide on *N*-benzylimine compound **5** derived



Scheme 1.

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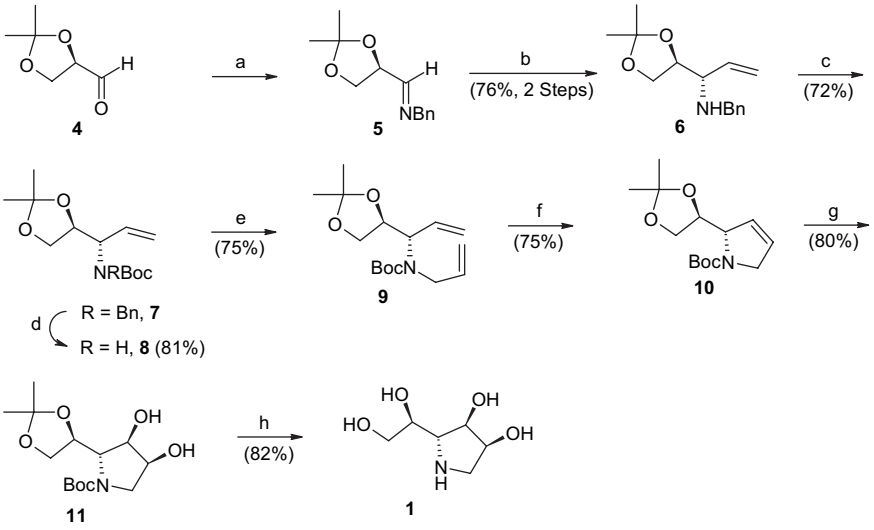
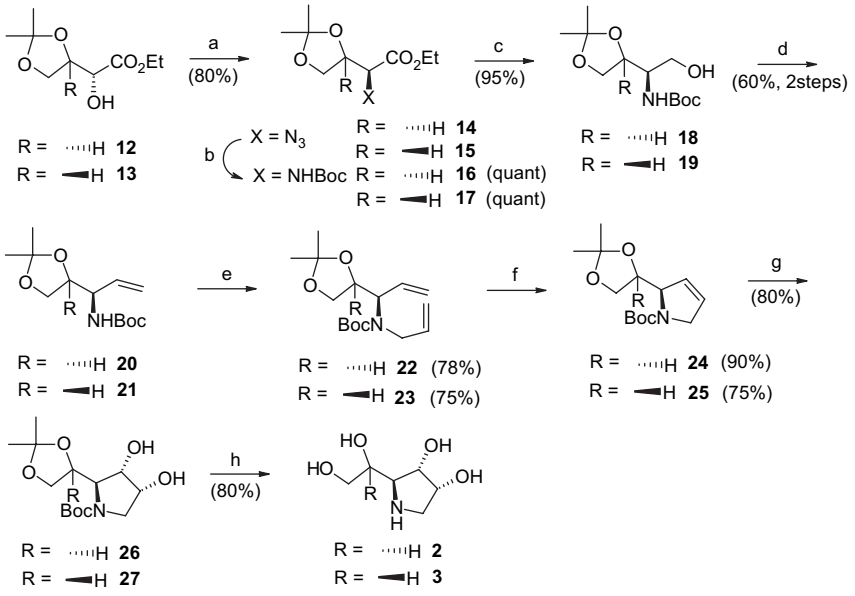
from commercially available (*R*)-2,3-*O*-isopropylidene glyceraldehyde **4**.[6] Treatment of compound **6** with Boc_2O in the presence of Et_3N afforded **7**, which when subjected to Li/liq. NH_3/THF conditions gave compound **8** as a white solid. Allylation of **8** under standard reaction conditions (NaH, ally bromide, in DMF) gave **9**. The diene **9** on reaction with Grubbs' first generation[4a,7] catalyst in DCM gave the expected pyrroline **10** in 75% yield. Subsequent diastereoselective dihydroxylation[8] of **10** with OsO_4 yielded the compound **11** as an exclusive isomer. Compound **11** was converted into imino sugar **1** as its HCl salt, by treatment with HCl in methanol,[9] whose spectral and physical data were in good agreement with the literature values (Scheme 2).[3j]

The synthesis of **2** starts from ethyl 3,4-*O*-methylidine D-erythronate **12** prepared from D-isoascorbic acid (Scheme 3).[10] The triflate derivative of this compound was prepared in quantitative yield by treatment of **12** with Tf_2O, 2,6-lutidine, in DCM at −20 °C to 0 °C. This triflate derivative underwent a smooth S_N2 reaction with LiN_3 in DMF to give azide **14** in 80% yield. Reduction of **14** with TPP in THF–H_2O produced the amino ester, which was immediately protected as its NHBoc derivative **16** in quantitative yield. Compound **16** was converted to its NHBoc protected amino alcohol **18** using $LiAlH_4$. Dess–Martin periodinane oxidation of the primary alcohol function of **18** led to aldehyde. Unfortunately, efforts to convert aldehyde to an olefin compound were unsuccessful under standard Wittig and Tebbe[11] protocols.



Scheme 2. Reagents and conditions: (a) $BnNH_2$, anhyd $MgSO_4$, ether, 0 °C–rt, 2 h; (b) CH_2=CH–MgBr, ether, 0 °C–rt 15 h; (c) NEt_3, Boc_2O, CH_2Cl_2, 0 °C–rt, 24 h; (d) Li, liq. NH_3, THF, −50 °C, 1 h; (e) NaH, allyl bromide, DMF, 0 °C–rt, 12 h; (f) 10 mol % of Grubbs' first generation catalyst, CH_2Cl_2, rt, 12 h; (g) OsO_4, NMO monohydrate, acetone/H_2O (3:1), 12 h; and (h) methanol/HCl, rt, 10 h.



Scheme 3. Reagents and conditions: (a) i, Tf_2O, 2,6-lutidine, CH_2Cl_2, −20 to 0 °C, 45 min; ii, LiN_3, DMF, rt, 3 h; (b) TPP, THF/H_2O, 60 °C, 3 h then NEt_3, Boc_2O, 0 °C–rt, 12 h; (c) $LiAlH_4$, THF, 0 °C–rt, 30 min; (d) i, Dess–Martin periodinane, 0 °C–rt, 1.5 h; ii, Zn, CH_2I_2, $Ti(O^iPr)_4$, THF, rt, 1 h; (e) NaH, allyl bromide, DMF, 0 °C–rt, 12 h; (f) Grubbs' first generation catalyst, CH_2Cl_2, rt, 12 h; (g) OsO_4, NMO monohydrate, acetone/H_2O (3:1), 12 h; and (h) methanol/HCl, rt, 10 h.

Finally under Takai–Nozaki methylenation[12] conditions the olefin compound **20** was obtained in 60% overall yield (for two steps). Olefinic compound **20** was converted to the expected target molecule **2** by a similar reaction synthetic route that was carried out for the preparation of **1**.

For the synthesis of 1,4-dideoxy-1,4-imino-L-allitol **3** we selected α-hydroxy ester **13** as a starting material, which can be easily prepared from L-ascorbic acid by a reported procedure.[10] This α-hydroxy ester was converted into the hydroxy pyrroline derivative **27**, following a similar reaction pathway used for **26** (Scheme 3).

3. Conclusion

In summary, we have developed a short and efficient synthesis of 1,4-dideoxy-1,4-imino hexitols where the five membered core skeleton was constructed by ring-closing metathesis of different diastereomers of **I**. A simple and good yielding methodology for preparing different diasteromers of **I** has also been developed from readily available starting materials. The above approach is general and useful for the synthesis of further analogs. Its application in the synthesis of indolizidine alkaloids is in progress in our laboratories.

4. Experimental section

4.1. General

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as an eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FTIR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Gemini-200 MHz or Bruker Avance-300 MHz spectrometer. ^{1}H NMR data are expressed as chemical shifts in parts per million followed by multiplicities (s-singlet; d-doublet; t-triplet; q-quartet; and m-multiplet), number of proton(s), and coupling constant(s) *J* (Hz). ^{13}C NMR chemical shifts are expressed in parts per million. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.1.1. (3*S*,4*S*)-*N*-Benzyl-4,5-*O*-isopropylidene-4,5-dihydroxypent-1-en-3-amine 6. To a solution of (2*S*)-2,3-*O*-isopropylidene glyceraldehyde **4** (1.60 g, 12.30 mmol, 1 equiv) in dry ether (25 mL) and anhydrous $MgSO_4$ (2 g) was added benzylamine (1.38 g, 12.80 mmol, 1.04 equiv) in dry ether (25 mL) at 0 °C and stirred at room temperature for 2 h. The reaction mixture was filtered and concentrated to give crude imine **5**, which was used as such in the next step. To the solution of vinylmagnesium bromide prepared from Mg (3.29 g, 135.10 mmol, 11 equiv) and vinyl bromide (6.56 g, 61.40 mmol, 5 equiv) in THF (30 mL) was added the solution of chiral imine **5** in Et_2O (30 mL) over 30 min at 0 °C under nitrogen. After stirring for 15 h at room temperature, the mixture was poured into saturated NH_4Cl (150 mL) and extracted into ether (3×100 mL). The collected ether layers were combined washed with water, brine, then dried over Na_2SO_4, concentrated under reduced pressure, and purified through column chromatography (hexane/ethyl acetate, 94:6) to give **6** (2.30 g) in 76% (overall yield for two steps) as a colorless oil. $[\alpha]_D^{25}$ +17.17 (*c* 1, $CHCl_3$) [lit.[6] $[\alpha]_D^{25}$ +17.20 (*c* 1, MeOH)]; IR ν_{max} 2987, 1729, 1454, 1375, 1216, 1156, 852 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.35 (m, 5H), 5.55–5.70 (m, 1H), 5.15–5.30 (m, 2H), 4.05–4.15 (m, 1H), 3.80–3.95 (m, 4H), 3.60 (d, 1H, *J*=13.2 Hz), 3.15–3.20 (m, 1H), 1.40 (s, 3H), 1.30 (s, 3H); FABMS (*m*/*z*): 248 [M$^+$+1].

4.1.2. (3*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-4,5-*O*-isopropylidene-4,5-dihydroxypent-1-en-3-amine 8. To the starting material **6** (0.65 g, 2.60 mmol, 1 equiv) in dry DCM (10 mL) was added Et_3N (0.36 ml, 2.60 mmol, 1 equiv) followed by Boc_2O (1.5 mL, 6.50 mmol, 2.5 equiv) at 0 °C and continued stirring at room temperature for 24 h. The reaction mixture was washed with saturated NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The collected organic layers were combined washed with brine then dried over Na_2SO_4 and concentrated in vacuo and purified through silica gel column chromatography using hexane/ethyl acetate (97:3) to give **7** (0.66 g) in 72% as a syrup. Lithium (0.13 g, 18.70 mmol, 10.4 equiv) was added in small portions to the solution of starting material **7** (0.65 g, 1.80 mmol, 1 equiv) in THF (15 mL) and liquid ammonia at −50 °C until a blue solution was obtained. After 1 h saturated NH_4Cl (100 mL) was added and the ammonia was evaporated followed by extraction in ethyl acetate (3×50 mL). The collected organic layers were combined washed with brine and dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography using hexane/ethyl acetate (96:4) to give **8** (0.39 g) in 81% yield as a white solid. $[\alpha]_D^{25}$ −45.54 (*c* 0.9, $CHCl_3$); mp 65 °C; IR ν_{max} 1648, 1368, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.9–5.7 (m, 1H), 5.3–5.2 (m, 2H), 4.73 (br d, 1H, *J*=8.5 Hz), 4.25–4.05 (m, 2H), 4.0 (dd, 1H, *J*=6.8 and 8.5 Hz), 3.75 (dd, *J*=5.1 and 8.5 Hz), 1.44 (s, 9H), 1.4 (s, 3H), 1.31(s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155, 134, 117, 110, 80, 77.5, 66, 54.5, 28, 26, 24.5; FABMS (*m*/*z*): 258 [M$^+$+1].

4.1.3. (3*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-*N*-prop-1-enyl-4,5-*O*-isopropylidene-4,5-dihydroxypent-1-en-3-amine 9. To an ice cold solution of compound **8** (0.35 g, 1.36 mmol, 1 equiv) in DMF was added NaH (0.136 g, 2 mmol, 1.5 equiv) after 30 min stirring at room temperature, allyl bromide (0.29 mL, 3.33 mmol, 2.4 equiv) was added and stirred for 12 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl (25 mL) and extracted with ether (3×50 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a crude oil. Purification of the residual product by chromatography (hexane/ethyl acetate, 94:6) afforded **9** as a yellow oil (0.3 g, 75%). $[\alpha]_D^{25}$ −6.55 (*c* 0.9, $CHCl_3$); IR ν_{max} 1695, 1639, 1396, 1368, 1251, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6–5.7 (m, 2H), 5.4–5.0 (m, 4H), 4.3 (dd, 2H, *J*=6.6 and 13.4 Hz), 3.97 (dd, 1H, *J*=6.2 and 8.3 Hz), 3.85–3.65 (m, 3H), 1.45 (s, 9H), 1.39 (s, 3H), 1.32 (s, 3H); FABMS (*m*/*z*): 298 [M$^+$+1].

4.1.4. (1*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-5,6-*O*-isopropylidene-5,6-dihydroxy-2-pyrroline 10. Diene **9** (0.25 g, 0.8 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (250 mL). Grubbs' first generation catalyst (70 mg, 0.08 mmol, 0.1 equiv) was added and the resulting purple solution turned brown after 10 min. The reaction mixture was stirred at room temperature for 12 h, then concentrated in vacuo, the residue was purified by column chromatography (hexane/ethyl acetate, 9:1) and the title compound **10** was obtained as colorless oil (0.17 g, 75%). $[\alpha]_D^{25}$ −26.5 (*c* 0.6, $CHCl_3$); IR ν_{max} 2927, 1699, 1391, 1170, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.9–5.75 (m, 2H), 4.45 (m, 1H), 4.3–4.2 (m, 2H), 4.0–3.8 (m, 3H), 1.47 (s, 9H), 1.36 (s, 3H), 1.3 (s, 3H); FABMS (*m*/*z*): 270 [M^++1].

4.1.5. *N*-*tert*-Butoxycarbonyl-1,4-dideoxy-1,4-imino-5,6-isopropylidene-D-allitol 11. To a stirred solution of compound **10** (0.15 g, 0.5 mmol, 1 equiv) in acetone/H_2O (3 mL: 1 mL) was added NMO monohydrate (0.105 g, 0.78 mmol, 1.56 equiv) followed by OsO_4 (0.28 mL, 0.05 mmol, 0.1 equiv) at 0 °C and stirred at room temperature for 12 h. After addition of Na_2SO_3 (0.07 g, 0.55 mmol, 1.1 equiv) the acetone was removed under reduced pressure and the reaction mixture was diluted with water and extracted with DCM (3×25 mL). The combined organic layers were dried over Na_2SO_4 concentrated in vacuo purified by column chromatography (hexane/ethyl acetate, 6:4) to give compound **11** as colorless oil (0.14 g, 80%). $[\alpha]_D^{25}$ −36.48 (*c* 0.5, $CHCl_3$); IR ν_{max} 3493, 2980, 2927, 1671, 1405, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.4–4.0 (m, 4H), 4.0–3.8 (m, 1H), 3.75–3.6 (m, 1H), 3.6–3.35 (m, 2H), 2.75 (br s, 1H), 2.40 (br s, 1H), 1.50 (s, 9H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.1, 109.3, 80.1, 75.8, 72.7, 70.2, 67.4, 64.9, 51.3, 28.4, 26.2, 24.8; FABMS (*m*/*z*): 304 [M^++1].

4.1.6. 1,4-Dideoxy-1,4-imino-D-allitol 1. To the compound **11** (0.070 g, 0.23 mmol) was added the methanolic solution of HCl (1.7 M, 5 mL) and the mixture was stirred at room temperature for 10 h. After evaporation of the solvent, the resultant residue was recrystallized in ethanol to give **1** (0.04 g) in 82% yield as a salt. $[\alpha]_D^{25}$ +25.6 (*c* 0.9, H_2O); mp 109–110 °C [lit.[3j] $[\alpha]_D^{25}$ +25.6 (*c* 0.9, H_2O); mp 112–113 °C]; IR ν_{max} 3414, 2922, 1691, 1075 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 4.3–4.5 (m, 2H), 4.1–4.2 (m, 1H), 3.60–3.80 (m, 3H), 3.30–3.50 (m, 2H); ^{13}C NMR (D_2O, 75 MHz) δ 71.10, 70.80, 69.41, 63.32, 62.86, 50.93; FABMS (*m*/*z*): 164 [M^++1].

4.1.7. Ethyl (2*S*,3*S*)-2-azido-3,4-isopropylidenedioxybutanoate 14. To a solution of ethyl 3,4-*O*-methylidene D-erythronate **12** (2 g, 9.8 mmol, 1 equiv) prepared from D-isoascorbic acid in CH_2Cl_2 (20 mL) at −20 °C were added trifluoromethane sulfonic anhydride (2.1 mL, 12.73 mmol, 1.3 equiv) followed by 2,6-lutidine (1.47 mL, 12.73 mmol, 1.3 equiv). After 30 min stirring at this temperature the reaction mixture was poured into water (25 mL) and the layers were separated, aqueous layer was extracted with CH_2Cl_2 (2×25 mL), the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. To this triflate derivative in dry DMF (20 mL) was added 20% aqueous solution of LiN_3 (6 mL, 2.5 equiv) and the resulting yellow solution was stirred at room temperature for 3 h. The reaction mixture was diluted with water (20 mL) and extracted with diethylether (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate, 95:5) to give the title compound **14** as colorless oil (1.83 g, 80%). $[\alpha]_D^{32}$ −45 (*c* 1.1, CH_2Cl_2) [lit.[13] $[\alpha]_D$ −44 (*c* 1.1, CH_2Cl_2)]; IR ν_{max} 2987, 2113, 1744, 1455, 1192, 1063 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.5 (ddd, 1H, *J*=5 and 6.7 Hz), 4.3 (q, 2H, *J*=7.54 Hz), 4.1 (dd, 1H, *J*=8.4 and 6.7 Hz), 3.95 (dd, 1H, *J*=8.4 and 6.7 Hz), 3.65 (br d, 1H, *J*=4.2 Hz), 1.5 (s, 3H), 1.35 (s, 3H), 1.34 (t, 3H, *J*=7.5 Hz); HRMS (ESI) calcd for $C_9H_{15}N_3O_4Na$ $[M+Na]^+$ 252.0960, found 252.0949.

4.1.8. Ethyl (2*S*,3*S*)-2-(*tert*-butoxycarbonylamino)-3,4-isopropylidenedioxy-butanoate 16. To a stirred solution of compound **14** (1.8 g, 7.86 mmol, 1 equiv) in THF (20 mL), TPP (2.06 g, 7.86 mmol, 1 equiv) was added and the resulting mixture was refluxed for 2 h, to this reaction mixture was added H_2O (2 mL) and refluxed for another 1 h. Then the reaction mixture was cooled to 0 °C, NEt_3 (3.3 mL, 23.58 mmol, 3 equiv) followed by Boc_2O (1.8 mL, 7.86 mmol, 1 equiv) were added. After stirring for 12 h at room temperature the reaction mixture was diluted with ethyl acetate (50 mL) and water (20 mL), the layers were separated and the organic layer was washed with saturated aqueous NH_4Cl (2×20 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The resulting residue was chromatographed (hexane/ethyl acetate, 9:1) to give compound **16** as a colorless oil (2.38 g, 100%). $[\alpha]_D^{32}$ +2.23 (*c* 1.12, $CHCl_3$); IR ν_{max} 3452, 2982, 1718, 1503, 1164, 861 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.1 (br d, 1H, *J*=8.7 Hz), 4.5 (dt, 1H, *J*=6.3 and 2.4 Hz), 4.32–4.18 (m, 3H), 4.0 (dd, 1H, *J*=6.3 and 7.9 Hz), 3.76 (dd, 1H, *J*=7 and 8.5 Hz), 1.45 (s, 9H), 1.41 (s, 3H), 1.3 (s, 3H), 1.25 (t, 3H, *J*=7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170, 156, 109, 80, 75, 66, 61.5, 54, 29, 26, 24.5, 14.0; HRMS (ESI) calcd for $C_{14}H_{26}NO_6$ $[M+H]^+$ 304.1760, found 304.1765.

4.1.9. (2*S*,3*R*)-3-(*tert*-Butoxycarbonylamino)-1,2-isopropylidenedioxy-butan-4-ol 18. To the stirred suspension of $LiAlH_4$ (448 mg, 11.78 mmol, 1.5 equiv) in THF (20 mL) at 0 °C was added compound **16** (2.38 g, 7.86 mmol, 1 equiv) in THF (10 mL). After 30 min stirring at 0 °C the reaction mixture was quenched with H_2O (0.5 mL), 15% aqueous NaOH (0.5 mL), and H_2O (1.5 mL). The precipitate was filtered through Celite pad and washed with ethyl acetate (50 mL) and the filtrate was concentrated in vacuo, purified by flash column chromatography (hexane/ethyl acetate, 3:1) to give compound **18** as a colorless solid (2 g, 95%). $[\alpha]_D^{32}$ +19.4 (*c* 1.03, $CHCl_3$); mp 55 °C; IR ν_{max} 3392, 2984, 1695, 1502, 1258, 1076 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.0 (br d, 1H, *J*=4.53 Hz), 4.28 (dt, 1H, *J*=6.8 and 2.3 Hz), 4.0 (dd, 1H, *J*=6.8 and 8.3 Hz), 3.8–3.6 (m, 4H), 2.4 (br s, 1H, OH), 1.45 (s, 9H), 1.42 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 109, 80, 76.5, 66.5, 64, 52, 28.5, 26, 25; HRMS (ESI) calcd for $C_{12}H_{24}NO_5$ $[M+H]^+$ 262.1654, found 262.1651.

4.1.10. (3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-4,5-*O*-isopropylidene-4,5-dihydroxypent-1-en-3-amine 20. To the stirred solution of alcohol **18** (0.5 g, 1.91 mmol, 1 equiv) in

10 mL of CH_2Cl_2 at 0 °C was added Dess–Martin periodinane (1.22 g, 2.87 mmol, 1.5 equiv) and stirred for 1.5 h the reaction mixture was diluted with ether (50 mL) followed by washing with saturated $NaHCO_3$ solution (2×50 mL) and brine (2×20 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo to afford corresponding aldehyde, which was used as such for further reaction without any purification. To the stirred suspension of Zn (2.25 g, 34.58 mmol, 18 equiv) in freshly dried THF was added CH_2I_2 (1.54 mL, 19.1 mmol, 10 equiv) at 25 °C, after 30 min of stirring $Ti(O^iPr)_4$ (3.83 mL, 3.82 mmol, 2 equiv, 1 M solution in THF) is added and the resulting mixture was stirred at 25 °C for 30 min. A solution of aldehyde (0.496 g, 1.91 mmol, 1 equiv) in THF (10 mL) was added dropwise after being stirred for 1 h and the reaction mixture was diluted with ether (50 mL) and washed with 1 M HCl (2×50 mL), $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by column chromatography (hexane/ethyl acetate, 9:1) to afford compound **20** as a yellow oil (0.3 g, 60%, for two steps). $[\alpha]_D^{32}$ +24.3 (*c* 0.76, $CHCl_3$); IR ν_{max} 3352, 2982, 1712, 1498, 1166, 1064 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.8 (m, 1H), 5.3–5.1 (m, 2H), 4.7 (br d, 1H, *J*=7.5 Hz), 4.2 (m, 2H), 4.0 (dd, 1H, *J*=6.8 and 8.3 Hz), 3.7 (dt, 1H, *J*=6.8 and 8.3 Hz), 1.45 (s, 9H), 1.42 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6, 136, 116, 109, 80, 77, 66.2, 53.4, 28.3, 26.2, 25; HRMS (ESI) calcd for $C_{13}H_{24}NO_4$ $[M+H]^+$ 258.1705, found 258.1716.

4.1.11. (3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-*N*-prop-1-enyl-4,5-*O*-isopropylidene-4,5-dihydroxypent-1-en-3-amine 22. Treatment of olefin **20** (0.3 g) as described for the preparation of **9** gave title compound **22** as a yellow oil (0.27 g, 78%). $[\alpha]_D^{32}$ +21.428 (*c* 1.05, $CHCl_3$); IR ν_{max} 3431, 2952, 1681, 1420, 1357, 1255, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.8–5.6 (m, 2H), 5.2–5.0 (m, 4H), 4.4–4.32 (m, 2H), 3.95 (dd, 1H, *J*=6.2 and 8.5 Hz), 3.8 (m, 2H), 3.6 (m, 1H), 1.45 (s, 9H), 1.40 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156, 136, 133, 119, 116, 109.5, 80, 75, 66, 61, 49, 28, 26, 24.5; HRMS (ESI) calcd for $C_{16}H_{28}NO_4$ $[M+H]^+$ 298.2018, found 298.2030.

4.1.12. (1*R*,5*S*)-*N*-*tert*-Butoxycarbonyl-5,6-*O*-isopropylidene-5,6-dihydroxy-2-pyrroline 24. Diene **22** (0.27 g) was treated with Grubbs' first generation catalyst (75 mg, 0.09 mmol, 0.1 equiv) using similar procedure described above for the preparation of **10** to give pyrrolidine **24** as a colorless oil (0.22 g, 90%). $[\alpha]_D^{32}$ +97.08 (*c* 0.685, $CHCl_3$); IR ν_{max} 2980, 2929, 1702, 1395, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.0–5.8 (m, 2H), 4.8–4.5 (m, 2H), 4.3–4.16 (m, 1H), 4.0–3.9 (m, 2H), 3.63 (m, 1H), 1.47 (s, 9H), 1.42 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155, 127.6 and 127.3,* 126.5 and 126.2,* 109, 80, 76, 75, 65 and 64.5,* 54.5 and 54.2,* 28.5, 26, 24.5; HRMS (ESI) calcd for $C_{14}H_{24}NO_4$ $[M+H]^+$ 270.1705, found 270.1697. *Rotamers.

4.1.13. *N*-*tert*-Butoxycarbonyl-1,4-dideoxy-1,4-imino-5,6-isopropylidene-D-talitol 26. Dihydroxylation of compound **24** (220 mg) with OsO_4 and NMO monohydrate as described for **11** gave compound **26** as colorless oil (0.2 g, 80%). $[\alpha]_D^{32}$ +51.4 (*c* 0.5, $CHCl_3$); IR ν_{max} 3422, 2981, 1672, 1400, 1139, 1096, 879 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.7–4.5 (m, 1H), 4.35 (m, 1H), 4.1 (m, 1H), 3.9 (m, 2H), 3.7 (dd, 1H, *J*=6.0 and 8.3 Hz), 3.5–3.38 (m, 2H), 2.85 (br s, 1H, OH), 2.57 (br s, 1H, OH), 1.5 (s, 9H), 1.4 (s, 3H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.5, 109, 80, 76, 74, 70, 66, 62.8, 52.2, 28.3, 26, 25.2; HRMS (ESI) calcd for $C_{14}H_{26}NO_6$ $[M+H]^+$ 304.1760, found 304.1755.

4.1.14. 1,4-Dideoxy-1,4-imino-D-talitol 2. To compound **26** (0.1 g, 0.33 mmol, 1 equiv) was added methanolic HCl (1.7 M, 8 mL) and the mixture was stirred at room temperature for 12 h. After evaporation of the solvent, the syrupy material was recrystallized from MeOH to give compound **2** as its HCl salt (43 mg, 80%). $[\alpha]_D^{32}$ −50.0 (*c* 0.5, H_2O); mp 150–152 °C [lit.[3j] $[\alpha]_D$ −50.3 (*c* 0.5, H_2O), mp 152–154 °C]; IR ν_{max} 3448 (br), 1653, 767 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 4.3 (dt, 1H, *J*=1.3 and 3.8 Hz), 4.2 (dd, 1H, *J*=3.8 and 8.9 Hz), 3.95 (m, 1H), 3.73 (dd, 1H, *J*=3.8 and 11.4 Hz), 3.6 (dd, 1H, *J*=5.1 and 11.4 Hz), 3.52 (dd, 1H, *J*=3.8 and 8.9 Hz), 3.42 (dd, 1H, *J*=3.8 and 14 Hz), 3.31 (dd, 1H, *J*=1.3 and 12.7 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 72.16, 69.3, 67.8, 63.1, 61.9, 49.9; HRMS (ESI) calcd for $C_6H_{14}NO_4$ $[M+H]^+$ 164.0922, found 164.0919.

4.1.15. Ethyl (2*S*,3*R*)-2-azido-3,4-isopropylidenedioxybutanoate 15. This compound was obtained in 80% yield according to the procedure as described for the preparation of **14**. $[\alpha]_D^{32}$ −14.78 (*c* 1.15, $CHCl_3$) [lit.[14] $[\alpha]_D$ −14.7 (*c* 2.6, $CHCl_3$)]; IR ν_{max} 2987, 2112, 1743, 1373, 1256, 1191, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.4 (m, 1H), 4.25 (q, 2H, *J*=6.8 Hz), 4.1–3.9 (m, 3H), 1.44 (s, 3H), 1.34 (t, 3H, *J*=6.8 Hz), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.8, 110, 75.2, 65.5, 63, 62, 26.2, 25, 14.0; HRMS (ESI) calcd for $C_9H_{15}N_3O_4Na$ $[M+Na]^+$ 252.0960, found 252.0972.

4.1.16. Ethyl (2*S*,3*R*)-2-(*tert*-butoxycarbonylamino)-3,4-isopropylidenedioxy-butanoate 17. The procedure followed was identical with that described for the preparation of **16** to give compound **17** in quantitative yield. $[\alpha]_D^{32}$ +38.7 (*c* 0.685, $CHCl_3$); mp 61–62 °C; IR ν_{max} 3332, 2982, 1743, 1724, 1171, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.24 (br d, 1H, *J*=7.0 Hz), 4.4–4.15 (m, 4H), 4.15–3.96 (m, 2H), 1.44 (s, 9H), 1.38 (s, 3H), 1.31 (t, 3H, *J*=7.0 Hz), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170, 155, 110, 80, 76.4, 65.6, 61.6, 55.6, 28.2, 26.3, 24.8, 14; LCMS *m/z*: 326 $[M+Na]^+$.

4.1.17. (2*R*,3*R*)-3-(*tert*-Butoxycarbonylamino)-1,2-isopropylidenedioxy-butan-4-ol 19. This compound was prepared in 95% yield from **17** by using the same procedure as described for **18**. $[\alpha]_D^{32}$ +4.14 (*c* 0.725, $CHCl_3$); IR ν_{max} 3441, 2981, 1692, 1167, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.1 (br d, 1H, *J*=7.633 Hz), 4.1 (m, 2H), 3.8 (dd, 2H, *J*=6.8 and 8.5 Hz), 3.6 (m, 2H), 1.45 (s, 9H), 1.42 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156, 110, 80, 76, 67.5, 62.5, 54, 28, 26.5, 25; HRMS (ESI) calcd for $C_{12}H_{23}NO_5Na$ $[M+Na]^+$ 284.1473, found 284.1483.

4.1.18. (3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-4,5-*O*-isopropylidene-4,5-dihydroxypent-1-en-3-amine 21. The title compound was prepared in 60% yield according to the procedure described for the preparation of compound **20** (two steps).

$[\alpha]_D^{32}$ +44 (*c* 0.735, $CHCl_3$); spectral data were identical with that of its enantiomer **8**. HRMS (ESI) calcd for $C_{13}H_{23}NO_4Na$ $[M+Na]^+$ 280.1524, found 280.1534.

4.1.19. (3*R*,4*R*)-*N*-*tert*-Butoxycarbonyl-*N*-prop-1-enyl-4,5-*O*-isopropylidene-4,5-dihydroxypent-1-en-3-amine 23. Compound **23** was prepared in 75% yield from compound **21** following the procedure used for the preparation of its enantiomer **9**. $[\alpha]_D^{32}$ +7.2 (*c* 1.22, $CHCl_3$); spectroscopic properties of this compound were identical with those described for the enantiomer **9**. HRMS (ESI) calcd for $C_{16}H_{27}NO_4Na$ $[M+Na]^+$ 320.1837, found 320.1848.

4.1.20. (1*R*,5*R*)-*N*-*tert*-Butoxycarbonyl-5,6-*O*-isopropylidene-5,6-dihydroxy-2-pyrroline 25. This compound was prepared in 75% yield from **23** by using the same procedure as described for **10**. $[\alpha]_D^{32}$ +26.1 (*c* 1, $CHCl_3$); with spectroscopic data as for the enantiomer **10**. ESIMS *m*/*z*: 269 $[M]^+$.

4.1.21. *N*-*tert*-Butoxycarbonyl-1,4-dideoxy-1,4-imino-5,6-isopropylidene-L-allitol 27. The title compound **27** was obtained in 80% yield according to the procedure described for the preparation of **11**. $[\alpha]_D^{32}$ +35.5 (*c* 1, $CHCl_3$); spectral data were identical with that of its enantiomer. HRMS (ESI) calcd for $C_{14}H_{25}NO_6Na$ $[M+Na]^+$ 326.1579, found 326.1590.

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