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Enantioselective synthesis of hydroxylated pyrrolidines via Sharpless epoxidation and olefin metathesis

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Abstract—The enantioselective synthesis of polyhydroxylated pyrrolidines from enantiomerically pure 2,3-epoxy-pent-4-en-1-ol **5** is described herein. The epoxy alcohol, readily available in any configuration by Sharpless epoxidation, was submitted to regioselective C-3 ring-opening with allyl amine, Boc-protection and ring-closing metathesis to yield dehydropyrrole derivative **7**. From this key intermediate, 1,4-dideoxy-1,4-imino-D-ribitol (+)-**3** and 1,4-dideoxy-1,4-imino-D-allitol (+)-**4** were prepared in high yields. The enantiomers of these compounds can be obtained by the same sequence starting from an epoxy alcohol with the opposite configuration.

1. Introduction

Iminosugars, or azasugars, are compounds in which the ring oxygen of a monosaccharide has been replaced by an imino group. Many of these compounds and their deoxygenated derivatives are naturally occurring, including several powerful and specific glycosidase inhibitors.[1] The bioactivity of these molecules has been attributed to their ability to 'mimic' the oxocarbenium ion formed during the hydrolysis of the carbohydrate–glycosidic bond, as the heterocyclic nitrogen is positively charged at physiological pH.[2] As glycolysis is crucial to many biological processes, several iminosugars and related compounds have demonstrated activities against cancer, diabetes, and viral infections.[3] Although polyhydroxylated piperidines are structurally more similar to monosaccharides than polyhydroxylated pyrrolidines, the latter are also surprisingly active and selective glycosidase inhibitors.[1] Some representative examples are found in Figure 1.

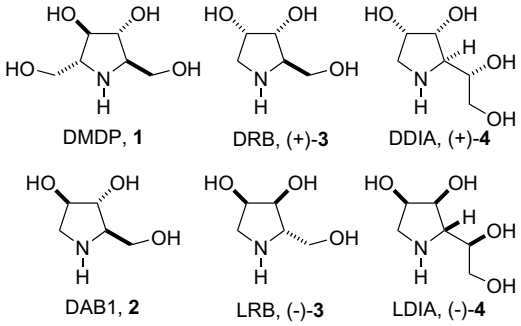

Figure 1. Glycosidase inhibitors with the polyhydroxylated pyrrolidine structure.

2,5-Dideoxy-2,5-imino-D-mannitol **1** (DMDP), one of the most widely occurring natural iminosugars, has been thoroughly studied.[4] 1,4-Dideoxy-1,4-imino-D-arabinitol **2** (DAB1), among the most important glycosidase inhibitors, is a promising therapeutic candidate.[5] 1,4-Dideoxy-1,4-imino-D-ribitol (+)-**3** (DRB), which was found in mulberry trees (*Morus alba*), is also a potent inhibitor of glucosidase and of eukaryotic DNA polymerases.[6] Its enantiomer, 1,4-dideoxy-1,4-imino-L-ribitol (−)-**3**, prepared for the first time in 1987 from mannose,[7j] has since been prepared by various syntheses and extensively studied.[7] Lesser well known are the corresponding dihydroxyethyl pyrrolidines. The β-glucosidase inhibitor 1,4-dideoxy-1,4-imino-D-allitol (+)-**4** can be isolated from natural sources such as glyceraldehydes and D-gulonolactone.[8] Its enantiomer (−)-**4** is a moderate inhibitor of human liver α-mannosidases, and demonstrates other biological activities.[9] The majority of the various reported synthetic routes to these compounds are based on the transformations of sugar derivatives.

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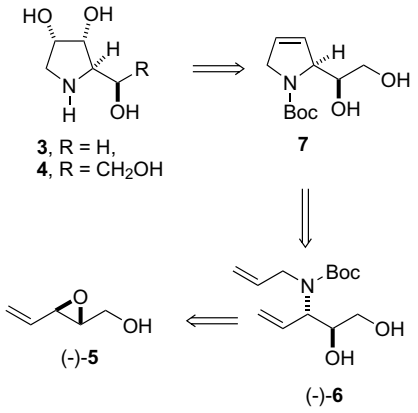


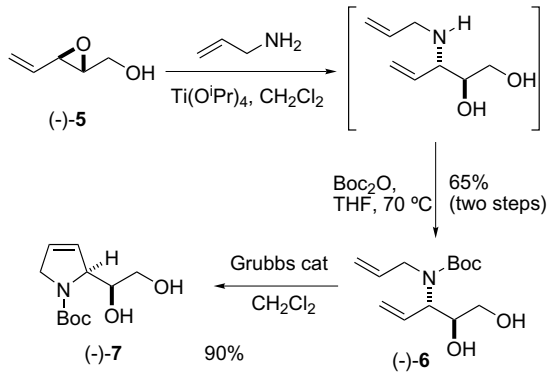
Figure 2. Retrosynthetic analysis of polyhydroxylated pyrrolidines.

Over the past few years, we have prepared several polyhydroxylated alkaloids (e.g., pyrrolines, piperidines, and indolizines)[10] starting from unsaturated epoxides, which are readily obtained through Sharpless epoxidation,[11] and subsequent ring-closing metathesis (RCM).[12,13] We envisioned that our strategy could be extended to prepare polyhydroxylated pyrrolidines **3** and **4** in any enantiomeric form starting from the proper enantiomer of unsaturated epoxide **5**. The retrosynthetic analysis of these compounds is shown in Figure 2. The desired compounds would be obtained from key intermediate **7** via side chain directed stereoselective dihydroxylation of the double bond. Compound **7** would in turn be synthesized by the RCM of amino diol **6**, the stereochemistry of which would be conveniently set by a nucleophilic C-3 ring-opening of enantiomerically enriched epoxide **5** using allyl amine.

2. Results and discussion

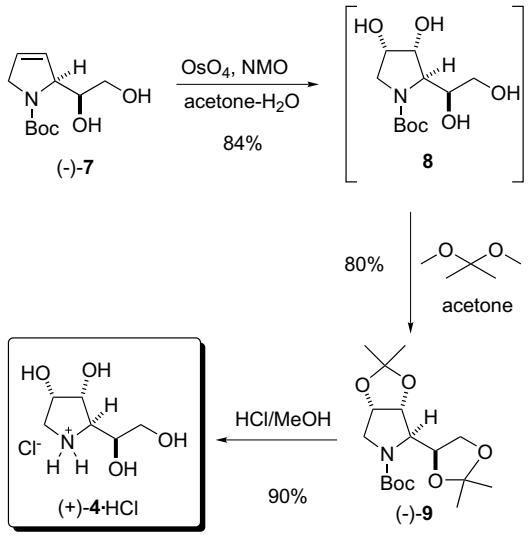
In line with our retrosynthetic analysis, we began the synthesis of the polyhydroxypyrrolidines by preparing epoxy alcohol **5**. Although this epoxide can be obtained by classical Sharpless asymmetric epoxidation of 2,4-pentadienol, we used the kinetic resolution methodology as developed by Jagger et al.[14] as it provides much higher enantiomeric excess. Sharpless epoxidation of the readily available bis-allylic alcohol 1,4-pentadien-3-ol followed by Payne rearrangement[15] afforded epoxy alcohol **5** in the desired configuration with >99% ee.

Subsequent regioselective and regiospecific ring-opening of **5** with allyl amine, followed by Boc protection, gave amino diol **6**. This reaction sequence required some development. Crotti's conditions[16] using a large excess of reagents (15 equiv of $LiClO_4$, and 10 equiv of allyl amine) at 60 °C gave the desired product in moderate yields as a mixture of regioisomers. Sharpless[17] conditions (2 mol of allylamine, 1 mol of $Ti(O^iPr)_4$ and room temperature) provided the corresponding amino diol with a total selectivity. Boc protection of the amine however was not straightforward; standard treatment with Boc_2O and base afforded compound **6** only in low yields. The best results were obtained using Boc_2O in THF at 70 °C without any base. Amino diol **6** was ultimately obtained from epoxy alcohol **5** in a 65% overall yield (Scheme 1).



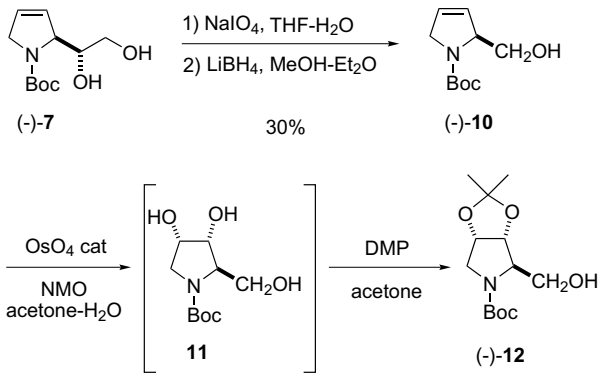
Scheme 1.

Treatment of (−)-**6** with first generation Grubbs's catalyst[12] (5–10%) in CH_2Cl_2 at room temperature gave key intermediate (−)-**7** in an excellent yield. Much to our satisfaction, dihydroxylation with catalytic OsO_4 and NMO[18] took place with a high diastereoselectivity *anti* to the dihydroxyethyl chain (only one diastereomer was observed by ^1H NMR). Subsequent protection of the vicinal diols with 2,2-dimethoxypropane afforded diastereomerically pure (−)-**9**. This protection facilitated the purification and characterization of the compound, which is highly polar and water soluble. Hydrolysis with HCl/MeOH cleanly afforded the hydrochloride of 1,4-dideoxy-1,4-imino-D-allitol (+)-**4**·HCl in a 90% yield (Scheme 2).[8]



Scheme 2.

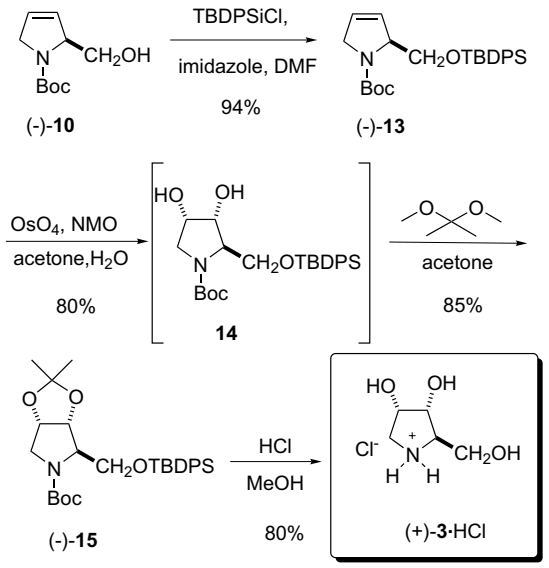
Our second synthetic target from intermediate (−)-**7** was 1,4-dideoxy-1,4-imino-D-ribitol (+)-**3**. Our first approach started with the synthesis of alcohol **10**. The oxidation of diol (−)-**7** with sodium periodate, followed by the reduction of the resulting aldehyde with DIBALH or $LiBH_4$, afforded alcohol (−)-**10** (Scheme 3). Since the transformation of **10** (although in racemic form) into DAB1 **2** has



Scheme 3.

described in the literature,[7e] the present approach constitutes a formal synthesis of enantiomerically enriched DAB1. Dihydroxylation with catalytic OsO_4 afforded compound **11** with a diastereomeric ratio of 10:1 (82%). Subsequent protection with 2,2-dimethoxypropane gave the diastereomerically pure (−)-**12** in a 95% yield. This compound[19] is a protected form of 1,4-dideoxy-1,4-imino-D-ribitol (+)-**3** and has previously been used in the synthesis of *trans*-2,3-*cis*-3,4-dihydroxyproline[20] and *epi*-swainsonine.[21]

In order to further improve the diastereomeric ratio of the dihydroxylation, we thought of protecting the alkoxy functionality of **10** with a bulky group, which would favor the approach of the osmium oxide toward the opposite side of the molecule. Thus, we protected compound **10** with a *tert*-butyl diphenylsilyl group in order to give compound **13** in an excellent yield (Scheme 4). As expected, dihydroxylation with OsO_4 gave diol **14** in a very high diastereomeric ratio (again, only one diastereomer observed by ^1H NMR). Protection with 2,2-dimethoxypropane to give acetal **15** facilitated the purification. Finally, hydrolysis of both protecting groups with HCl/MeOH yielded hydrochloride (+)-**3** in an 80% yield.



Scheme 4.

3. Conclusion

In conclusion, we have developed a novel synthetic route for the preparation of polyhydroxy pyrrolidines **3** and **4** starting from the enantiomerically enriched unsaturated epoxy alcohol **5**. Since the alcohol can be prepared in any configuration by asymmetric Sharpless epoxidation, both enantiomers of **3** and **4** are equally accessible.

4. Experimental

4.1. General methods

Optical rotations were measured at room temperature (23 °C) and concentrations were measured in g/100 mL. Infrared spectra were recorded using NaCl film. ^1H NMR Spectra were obtained at 400 MHz with tetramethylsilane as the internal standard. ^{13}C NMR Spectra were obtained at 100 MHz. Signal multiplicities were assigned by DEPT experiments. Chromatographic separations were carried out using SiO_2 (70–230 mesh) pre-treated with NEt_3 (2.5% v/v), and hexanes/ethyl acetate mixtures as the eluent. Compound **5** was prepared according to known procedures.[14]

4.2. (2*S*,3*S*)-3-(*N*-Allyl-*N*-*tert*-butoxycarbonyl)-4-penten-1,2-diol (−)-6

To a solution of epoxide (−)-**5** (2.3 g, 23 mmol) in CH_2Cl_2 (100 mL) were added allyl amine (6.9 mL, 92 mmol) and titanium isopropoxide (13.7 mL, 46 mmol). The reaction was monitored by TLC. After 48 h, 10 mL of 10% NaOH was added, and stirring was maintained for 24 h. The suspension was filtered, and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were dried over $MgSO_4$. The solvent was evaporated, and the resulting residue dissolved in THF (50 mL). Boc_2O (5.52 g, 25.3 mmol) was then added, and the mixture was heated at 70 °C for 15 h. Evaporation of the solvent followed by chromatographic purification yielded 3.8 g of (−)-**6** (65%) as a yellow oil. $[\alpha]_D = -22.6$ (*c* 1.0, $CHCl_3$). IR (film, ν_{max}) 3419, 1669, 1559, 1456, 1368 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (m, 1H), 5.78 (m, 1H), 5.23 (m, 2H), 5.12 (m, 2H), 4.19 (br s, 1H), 3.79 (m, 2H), 3.59 (s, 2H), 3.20 (s, 1H), 3.05 (br s, 1H), 2.79 (br s, 1H), 1.46 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5 (CO), 134.8 (CH), 134.4 (CH), 119.8 (CH_2), 117.2 (CH_2), 81.2 (C), 72.5 (CH), 63.4 (CH_2), 61.0 (CH), 49.9 (CH_2), 25.5 (CH_3) ppm. MS (EI) *m*/*z*: 202.2 [(M−55), 100%], 258.1 [$(M+H)^+$, 64%]. HRMS (*m*/*z*): calcd for $C_{13}H_{24}NO_4$, 258.1708. Found: 258.1705.

4.3. (2*S*)-*N*-*tert*-Butoxycarbonyl-2-[(1′*S*)-1′,2′-dihydroxyethyl]-2,5-dihydropyrrole (−)-7

To a stirred solution of (−)-**6** (0.53 g, 2.06 mmol) in CH_2Cl_2 (150 mL) was added a solution of Grubbs's catalyst (0.21 g, 0.17 mmol) in CH_2Cl_2 (100 mL). The solution was heated at 40 °C for 4 h. Evaporation of the solvent followed by chromatographic purification yielded 0.42 g of (−)-**7** (90% yield) as a brown oil. $[\alpha]_D = -108.1$ (*c* 0.97,

$CHCl_3$). IR (film, ν_{max}) 3855, 1696, 1676, 1456, 1368 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 4.74 (m, 1H), 4.32 (s, 1H), 4.20 (d, $J = 7.8$ Hz, 1H), 4.01 (dd, $J = 2.3$, 5.6 Hz, 1H), 3.76 (m, 1H), 3.59 (m, 2H), 3.10 (s, 1H), 2.09 (s, 1H), 1.48 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9 (CO), 128.3 (CH), 126.6 (CH), 81.2 (C), 75.1 (CH), 67.3 (CH_2), 63.2 (CH), 54.7 (CH_2), 28.6 (CH_3). ppm. MS (EI) m/z: 112.1 [(M−117), 100%]. HRMS calcd for $C_{11}H_{19}NO_4$: 229.1315. Found: 229.1314.

4.4. 1,4-Dideoxy-1,4-imino-D-allitol bis-isopropylidene acetal (−)-9

To a solution of (−)-**7** (0.05 g, 0.21 mmol) and NMO monohydrate (0.065 g, 0.48 mmol) in acetone (6 mL) and H_2O (0.6 mL) was added a 0.05 M solution of OsO_4 in ^{t}BuOH (0.22 mL, 0.017 mmol). After 48 h of stirring at room temperature, $Na_2S_2O_3$ (0.14 g, 0.88 mmol) was added, and the mixture was allowed to continue stirring. After 2 h, $MgSO_4$ was added, the suspension was filtered over Celite, and the solvent was evaporated to yield **8** (0.05 g, 0.02 mmol). The resulting crude was dissolved in acetone (5 mL) and 2,2-dimethoxypropane (8 μL, 0.06 mmol), and a catalytic amount of *p*-toluenesulfonic acid was added. The mixture was stirred at room temperature for 4 h, and monitored by TLC. CH_2Cl_2 (5 mL) was then added, and the solution then washed with saturated aq $NaHCO_3$ (3 × 5 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated. Chromatographic purification of the crude yielded 0.035 g of (−)-**9** (80% yield) as a yellow oil. $[\alpha]_D = -58.5$ (*c* 1.0, $CHCl_3$). IR (film, ν_{max}) 2983, 1697, 1405, 1369, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.71 (m, 2H), 4.35 (m, 1H), 4.11 (m, 2H), 3.86 (m, 2H), 3.42 (ddd, $J = 4$, 12.8, 34 Hz, 1H), 1.46 (s, 6H), 1.43 (s, 6H), 1.31 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 (CO), 111.8 (C), 110.1 (C), 81.5 (CH), 80.5 (CH), 80.22 (CH), 79.5 (CH), 75.6 (C), 66.7 (CH), 53.3 (CH_2), 28.6 (CH_3), 27.1 (CH_3), 26.7 (CH_3) ppm. MS (CI–NH_3) m/z: 344.0 [$(M+H)^+$, 61%], 288.1 [(M−56), 100%]. Anal. Calcd for $C_{17}H_{29}NO_6$: C, 59.46; H, 8.51; N, 4.08. Found: C, 59.47; H, 8.68; N, 4.02.

4.5. 1,4-Dideoxy-1,4-imino-D-allitol hydrochloride (+)-4

A solution of (−)-**9** (0.1 g, 0.03 mmol) in HCl/MeOH (2 mL) was stirred at room temperature until no starting material was observed by TLC (ca. 5 h). The solvent was removed and the crude triturated with Et_2O (3 × 3 mL) to yield 0.06 g of (+)-**4** (95% yield) as a white solid. Mp = 110–111 °C. $[\alpha]_D = +28.4$ (0.6, H_2O). (Lit[8e] $[\alpha]_D = +29.4$ (*c* 0.56, H_2O)). ^1H NMR (400 MHz, D_2O) δ 4.29 (dd, $J = 4.4$, 12.4 Hz, 1H), 4.25 (dd, $J = 2.4$, 4.6 Hz, 1H), 4.01 (dd, $J = 3.6$, 5 Hz, 1H), 3.61 (d, $J = 4$ Hz, 2H), 3.55 (dd, $J = 3.2$, 8 Hz, 1H), 3.33 (dd, $J = 3.6$, 12.8 Hz, 1H), 3.24 (dd, $J = 1.6$, 12.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, D_2O) δ 70.3 (CH), 69.9 (CH), 68.6 (CH), 62.5 (CH_2), 61.9 (CH), 50.1 (CH_2) ppm. MS (CI–NH_3) m/z: 164.0 [(M−35), 100%]. HRMS calcd for $C_7H_{14}NO_4$: 164.0922. Found: 164.0919.

4.6. (2*S*)-*N*-*tert*-Butoxycarbonyl-2-hydroxymethyl-2,5-dihydro-1*H*-pyrrole (−)-10

To a solution of aminodiol (−)-**7** (0.13 g, 0.57 mmol) in THF (1 mL) and H_2O (3 mL) was added $NaIO_4$ (0.18 g, 0.85 mmol). The mixture was stirred until no starting material was observed by TLC (ca. 2 h). H_2O (10 mL) was then added, and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were dried over $MgSO_4$ and dried by evaporation. The crude was dissolved in a mixture of MeOH (1 mL) and Et_2O (10 mL). To this solution was added $LiBH_4$ (0.02 g, 0.85 mmol). The mixture was stirred for 4 h and monitored by TLC. HCl (3 M, 2 mL) was added, and the mixture washed with Et_2O (3 × 5 mL). The aqueous layer was basified with saturated aq $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 5 mL). The organic phases were dried over $MgSO_4$, and the solvent was evaporated. Chromatographic purification of the crude yielded 0.04 g of (−)-**10** (30% yield) as a yellow oil. $[\alpha]_D = -124.6$ (*c* 1.0, $CHCl_3$). IR (film, ν_{max}) 3416, 1697, 1407, 1367, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (dd, $J = 1.6$, 6.4 Hz, 1H), 5.63 (dd, $J = 2$, 6.4 Hz, 1H), 4.73 (s, 1H), 4.08 (m, 2H), 3.76 (d, $J = 10.4$ Hz, 1H), 3.56 (dd, $J = 7.6$, 11.6 Hz, 1H), 1.58 (s, 1H), 1.49 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (CO), 127.0 (CH), 126.9 (CH), 80.8 (C), 67.9 (CH_2), 67.5 (CH), 54.4 (CH_2), 28.7 (CH_3) ppm. MS (CI–NH_3) m/z: 200.1 [$(M+H)^+$, 95%], 144.0 [(M−56), 100%]. HRMS calcd for $C_{10}H_{18}NO_3$: 200.1286. Found: 200.1283.

4.7. (2*R*,3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-2-hydroxymethyl-3,4-isopropylidendioxy-pyrrolidine (−)-12

To a solution of (−)-**10** (0.5 g, 0.25 mmol) and NMO monohydrate (0.07 g, 0.55 mmol) in acetone (9 mL) and H_2O (1 mL) was added 0.4 mL of a 0.05 M solution of OsO_4 in ^{t}BuOH (0.02 mmol). The mixture was stirred until no starting material was observed by TLC (ca. 24 h). $Na_2S_2O_3$ (0.05 g, 0.3 mmol) was added and, after 2 h, $MgSO_4$ was also added. The suspension was filtered over Celite and the solvent was removed at reduced pressure. The crude (0.05 g, 82% yield) showed a 10:1 diastereomeric ratio of triol **11** by ^1H NMR and ^{13}C NMR. This crude (0.05 g) was dissolved in acetone (5 mL) and 2,2-dimethoxypropane (0.07 mL, 0.54 mmol), and a catalytic amount of *p*-toluenesulfonic acid was added to the solution. The mixture was stirred until no starting material was observed by TLC (ca. 4 h). CH_2Cl_2(5 mL) was then added, and the organic layer washed with saturated aq $NaHCO_3$ (3 × 5 mL). The organic phase was dried over $MgSO_4$, and the solvent was evaporated. Chromatography of the crude afforded 0.06 g of diastereomerically pure (−)-**12** (95% yield) as a colorless oil. $[\alpha]_D = -30.3$ (*c* 0.3, $CHCl_3$). IR (film, ν_{max}) 3448, 2990, 2927, 1697, 1410 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$) δ 4.27 (m, 2H), 3.76 (m, 3H), 3.51 (m, 2H), 1.46 (s, 9H), 1.25 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CHCl_3$) δ 158.0 (CO), 111.9 (C), 82.0 (CH), 80.4 (C), 79.1 (CH), 65.2 (CH_2), 63.7 (CH), 57.2 (CH_2), 27.1 (CH_3), 21.5 (CH_3) ppm. MS (CI–NH_3) m/z: 438 [(M−56), 100%].

4.8. (2*R*)-*N*-*tert*-Butoxycarbonyl-2-*tert*-butyldiphenylsilyloxymethyl-2,5-dihydro-1*H*-pyrrole (−)-13

To a solution of (−)-**10** (0.25 g, 1.18 mmol) and imidazole (0.2 g, 2.95 mmol) in DMF (10 mL) was added *tert*-butylchlorodiphenylsilane (0.37 mL, 0.39 mmol). The mixture was stirred until no starting material was observed by TLC (ca. 24 h). Water (10 mL) was added, and the mixture was extracted with Et_2O (3 × 5 mL). The organic solution was dried over $MgSO_4$, the solvent was evaporated, and the crude was chromatographed to yield 0.5 g of (−)-**13** (94% yield) as a colorless oil. $[\alpha]_D = -24.6$ (1, $CHCl_3$). IR (film, ν_{max}) 2924, 2831, 1701, 1455, 1113 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$) δ 7.71 (m, 5H), 7.41 (m, 5H), 5.88 (m, 2H), 4.22 (m, 1H), 4.03 (ddd, $J = 4.8$, 5.6, 19.9 Hz, 2H), 3.83 (ddd, $J = 2.8$, 8.0, 26.3 Hz, 1H), 3.67 (dd, $J = 6.8$, 9.2 Hz, 1H), 1.47 (s, 9H), 1.02 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CHCl_3$) δ 154.1 (CO), 135.5 (CH), 134.7 (CH), 133.5 (CH), 129.5 (CH), 128.6 (CH), 127.6 (CH), 126.2 (CH), 79.4 (C), 65.5 (CH_2), 63.6 (CH), 54.2 (CH_2), 28.5 (CH_3), 26.7 (CH_3), 19.3 (C) ppm. MS (CI–NH_3) *m*/*z*: 438.2 [(M+H)$^+$, 100%], 338.1 [(M−99), 40%]. HRMS calcd for $C_{26}H_{36}NO_3Si$: 438.2464. Found: 438.2463.

4.9. (2*R*,3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-2-*tert*-butyldiphenylsilyloxymethyl-3,4-dihydroxypyrrolidine (−)-14

To a solution of (−)-**13** (0.5 g, 1.11 mmol) and NMO monohydrate (0.33 g, 2.44 mmol) in acetone (20 mL) and H_2O (2 mL) was added 1.78 mL of a 0.05 M solution of OsO_4 in ^{t}BuOH (0.09 mmol). The mixture was stirred until no starting material was observed by TLC (ca. 48 h). $Na_2S_2O_3$ (1.0 g, 6.3 mmol) was then added and, after 2 h, $MgSO_4$ was also added. The suspension was filtered over Celite, and the solvent was evaporated. The crude was chromatographed to afford 0.42 g of diastereomerically pure (−)-**14** (80% yield) as a colorless oil. $[\alpha]_D = -15.1$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max} 3396, 2930, 2857, 1696, 1426 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$) δ 7.64 (m, 5H), 7.39 (m, 5H), 4.39 (m, 2H), 3.89 (m, 3H), 3.72 (d, $J = 3.6$ Hz, 1H), 3.56 (d, $J = 4.8$ Hz, 1H), 2.78 (br s, 2H), 1.45 (s, 9H), 1.05 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CHCl_3$) δ 154.9 (CO), 139.3 (CH), 135.7 (CH), 134.5 (CH), 134.3 (CH), 130.1 (CH), 128.1 (CH), 80.3 (C), 80.1 (CH), 74.9 (CH), 69.9 (CH_2), 63.7 (CH), 51.5 (CH_2), 28.5 (CH_3), 26.7 (CH_3), 19.3 (C) ppm. MS (EI) *m*/*z*: 473.1 [(M+H)$^+$, 100%], 416.9 [(M−56), 60%]. HRMS calcd for $C_{26}H_{38}NO_5Si$: 472.2519. Found: 472.2522.

4.10. (2*R*,3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-2-*tert*-butyldiphenylsilyloxymethyl-3,4-isopropylidendioxy-pyrrolidine (−)-15

To a solution of (−)-**14** (0.2 g, 0.42 mmol) in acetone (10 mL) were added 2,2-dimethoxypropane (0.1 mL, 0.85 mmol) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred until no starting material was observed by TLC (ca. 4 h). CH_2Cl_2 (5 mL) was then added, and the organic layer washed with saturated aq $NaHCO_3$ (3 × 5 mL). The organic phase was dried over $MgSO_4$, and the solvent evaporated. Chromatography of the crude afforded 0.17 g of diastereomerically pure (−)-**15** (85% yield) as a white solid. Mp 79–80 °C. $[\alpha]_D = -36.1$ (*c* 1.05, $CHCl_3$). IR (film) ν_{max} 1696, 1403, 1175, 1112, 1055 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$) δ 7.63 (m, 5H), 7.41 (m, 5H), 4.78 (m, 2H), 4.12 (m, 2H), 4.03 (m, 1H), 3.68 (m, 2H), 1.49 (s, 6H), 1.37 (s, 9H), 1.05 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CHCl_3$) δ 154.2 (CO), 135.8 (CH), 132.9 (CH), 130.2 (CH), 130.0 (CH), 128.2 (CH), 128.1 (CH), 111.6 (C), 83.5 (CH), 82.9 (CH), 79.9 (CH_2), 64.8 (CH), 54.4 (CH_2), 28.7 (CH_3), 27.3 (CH_3), 25.3 (CH_3), 19.3 (C) ppm. MS (CI–NH_3) *m*/*z*: 512.5 [(M+H)$^+$, 100%], 455.7 [(M−56), 93%]. Anal. Calcd for $C_{29}H_{41}NO_5Si$: C, 68.00; H, 8.27; N, 2.78. Found: C, 68.07; H, 8.08; N, 2.74.

4.11. 1,4-Dideoxy-1,4-imino-D-ribitol hydrochloride (+)-3

A solution of (−)-**15** (0.085 g, 0.16 mmol) in HCl/MeOH (3 mL) was stirred at room temperature until no starting material was observed by TLC (ca. 5 h). The solvent was removed, and the crude triturated with Et_2O (3 × 3 mL) to yield 0.025 g of (+)-**3** (80% yield) as a white solid. Mp 129–130 °C. $[\alpha]_D = +53.9$ (*c* 1.0, H_2O). IR (film, ν_{max}) 3404, 1617, 1406, 1139, 1041 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, δ) 4.26 (ddd, $J = 2$, 3.9, 4 Hz, 1H), 4.13 (dd, $J = 3.6$, 8 Hz, 1H), 3.92 (dd, $J = 3.2$, 12.3 Hz, 1H), 3.76 (dd, $J = 5.6$, 12 Hz, 1H), 3.56 (m, 1H), 3.40 (dd, $J = 4$, 12.4 Hz, 1H), 3.30 (m, 1H), 3.26 (dd, $J = 1.8$, 13 Hz, 1H) ppm. ^{13}C NMR (100 MHz, CD_3OD, δ) 71.8 (CH), 69.9 (CH), 62.8 (CH), 58.3 (CH_2), 49.9 (CH_2) ppm. MS (CI–NH_3) *m*/*z*: 134.1 [(M−35), 100%]. Anal. Calcd for $C_5H_{12}NO_3Cl$: C, 35.41; H, 7.13; N, 8.26. Found: C, 35.30; H, 6.86; N, 7.89.

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