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Full Paper

Synthesis of (*R*)-Dihydropyridones as Key Intermediates for an Efficient Access to Piperidine Alkaloids

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Abstract: The efficient transformation of *D*-glucal to (2*R*)-hydroxymethyldihydropyridinone **5** in seven steps and 35 % overall yield is reported. Dihydropyridone **5** constitutes a versatile chiral building block for the synthesis of various piperidine alkaloids. In this regard, **5** was converted to piperidinol **13** and piperidinone **15**, that may be further elaborated for the syntheses of (+)-desoxoprosophylline (**1**) and deoxymannojirimycin (**3**) or *D*-mannolactam (**4**), respectively.

Keywords: Dihydropyridones, piperidine alkaloids, azasugars, asymmetric synthesis

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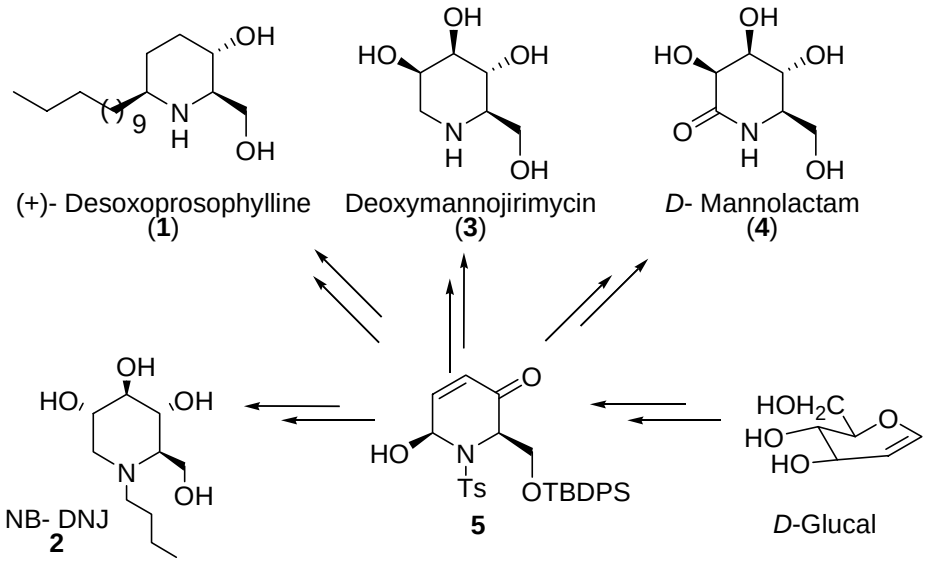
Introduction

Piperidine alkaloids comprise a large family of compounds that exhibit a large spectrum of biological activities of medicinal interest. In particular, alkaloid lipids such as (+)-desoxoprosophylline (**1**, Figure 1) [1] display significant anesthetic, analgesic and antibiotic activities [2-4], while their corresponding iminosugars – exemplified by N-butyl–1–deoxynojirimycin (NB-DNJ, **2**) which was recently approved for the treatment of Gaucher disease [5] – constitute promising leads for the development of immunosuppressive [6], antiviral [7], antidiabetic [8] and antitumour agents [9]. In

addition, deoxymannojirimycin (**3**) and D-mannolactam (**4**, Figure 1) have also shown to inhibit various enzymes that participate in the binding and processing of diverse glycoproteins, underlying their possible therapeutic values [10-12].

Figure 1. Piperidine Alkaloids and Key Intermediate Dihydropyridone **5**.



As a result intense research efforts have been devoted to the development of methodologies and synthetic strategies for the efficient preparation of these compounds and derivatives. Most of these methods utilize sugars or amino acids as their chiral pool synthons [13-19] and suffer from a lack of selectivity and applicability to diverse compounds. On the other hand, the optically active 1,6-dihydro-2*H*-pyridin-3-ones represent flexible building blocks for the efficient access to diverse multi-functionalized bioactive indolizines, quinolizidines and piperidine alkaloids [20]. Recently, we reported the preparation of (2*S*)–hydroxymethyldihydropyridinone, [21] a chiral key intermediate for the synthesis of various piperidine alkaloids such as (–)–desoxoprosophylline, allonojirimycin and indolizidine alkaloids (e.g. swainsonine). The common structural feature of all the aforementioned molecules is the (*S*)-configuration at C–2. Herein we present an efficient and highly enantioselective route to its (*R*)−enantiomer **5** starting from the commercially available *D*-glucal. This molecule represents a key intermediate for the synthesis of broad variety natural and unnatural piperidine alkaloids and/or iminosugars displaying an (*R*)–configuration at C–2.

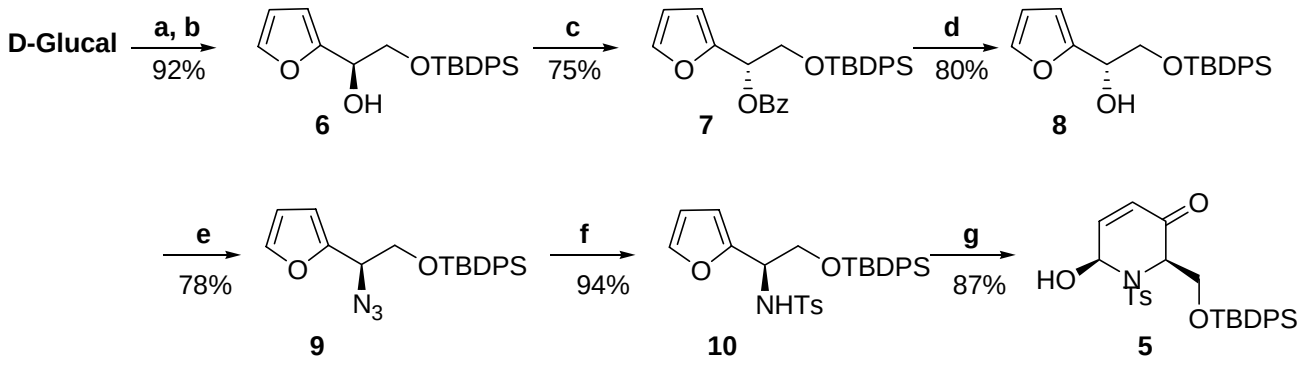
Results and Discussion

The key step for the implementation of the proposed synthetic sequence is the synthesis of chiral (*R*)-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-furan-2-yl-ethyl]-4-methylbenzenesulfonamide (**10**), since all final products retain that stereochemistry. Commercially available *D*-glucal was used as strarting material for the synthesis of this intermediate. More specifically, *D*-glucal was reacted with $HgSO_4$ (as a solution in 0.002 M H_2SO_4) and subsequently its primary hydroxy group was protected with TBDPSCl to provide the 2–furyl glycol (+)−**6**, according to a literature procedure reported by Hauser *et al*. (Scheme 1) [22].

The stereochemistry of compound **6** was efficiently inverted using the Mitsunobu protocol (DEAD, Ph_3P, benzoic acid) affording the (*S*)-ethyl-2-(*tert*-butyldiphenylsilanyloxy)-1-furan-2-yl-benzoate **7**, which was further saponified to afford (*S*)-1-furan-2-yl-ethanol **8**. The displacement of the secondary hydroxy group with azide with inversion of configuration was performed in high enantiomeric excess (>98%) on treating **8** with DBU in toluene and DPPA. The enantiomeric excess was determined by hydrogenating compound **9** over 10% Pd/C (4 mg) under 1 bar pressure for 40 min [23]. The mixture was filtered over Celite® and the amine was then derivatized by adding Et_3N and (–)-menthyl chloroformate. The ratio of enantiomers was determined by reversed-phase HPLC [Kromasil 100-5, C-18, H_2O/MeOH/CH_3CN gradient elution from 40:40:20 to 0:10:90, flow = 1.2 mL/min, UV detection at 238 nm]; t_R major 48 min (97%); and t_R minor 49.4 min (3%).

Hydrogenation of **9** over Pd/C and tosylation of the resulting amine afforded the *N*-furfuryl-sulfonamide (*R*)-**10**. Finally, oxidative cyclization of compound **10** using a modified version of the standard aza-Achmatowich rearrangement conditions furnished the target dihydropyridone **5**.

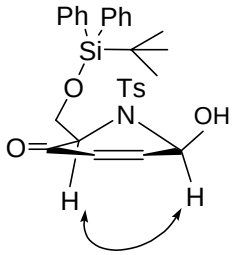
Scheme 1. Synthesis of Key Intermediate Dihydropyridone **5**.



Reagents and Conditions. (a) $HgSO_4$, H_2SO_4, MeOH; (b) TBDPSCl, imidazole, DMAP, DMF; (c) DEAD, PPh_3, $PhCO_2H$, THF; (d) MeOH, aqueous NaOH; (e) DPPA, DBU, toluene, O °C; (f) 1. H_2, Pd/C, EtOAc; 2. TsCl, Et_3N, CH_2Cl_2; (g) *m*-CPBA, CH_2Cl_2.

The diastereomeric purity of the product was revealed by ^{1}H-NMR and HPLC, since the presence of the other diastereoisomer was not detected, while the stereochemistry of the newly formed stereocenter was determined by 2D-NOESY spectroscopic analysis (the absolute configuration at C-2 derives from the starting material). Thus, the clear strong cross peak observed between the protons on C-2 and C-6 is indicative of their *cis pseudo*-diaxial conformation (Figure 2). Furthermore, the observed NOE between the aromatic protons of the tosyl group and the protons of *tert*-butyldiphenyl-silanyloxymethyl group confirmed this configuration. Finally, the observed optical rotation value for this compound ($[\alpha]_D^{22}$ –25.5) constitutes additional proof of the assigned configuration, since its enantiomer displays the opposite sign ($[\alpha]_D^{22}$ +27.9) [20b].

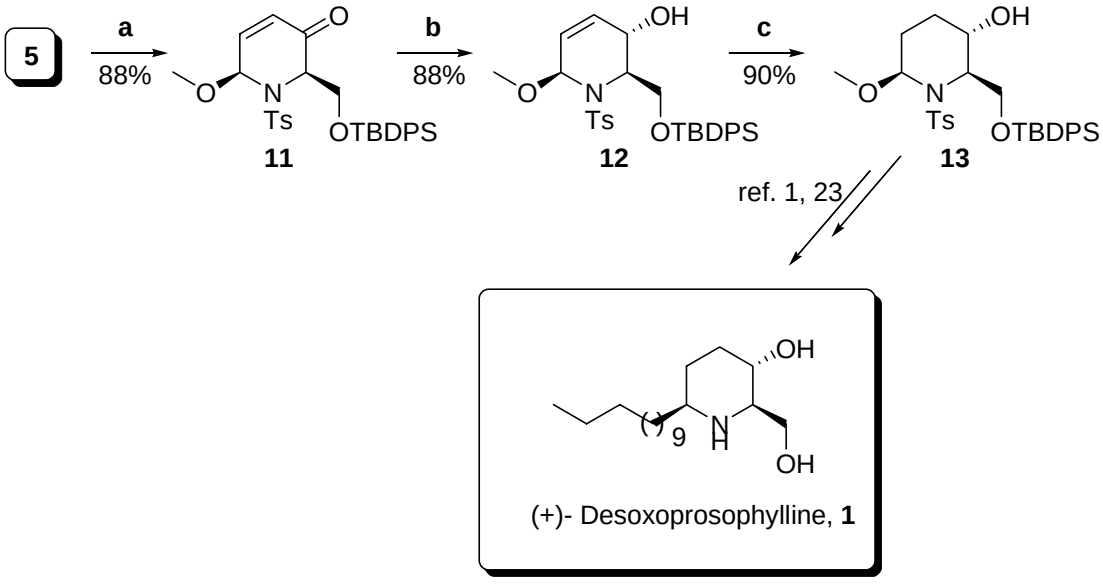
Figure 2. NOE Correlations in **5**.



As depicted in Scheme 2, dihydropyridone **5** was treated with $HC(OMe)_3$ in the presence of $BF_3{\cdot}OEt_2$ to furnish acetal **11**, which under modified Luche reduction conditions ($NaBH_4$, $CeCl_3$) was converted to allylic alcohol **12**. Subsequent catalytic hydrogenation of alcohol **12** produced piperidinol **13**, whose configuration was elucidated by 2D-COSY and NOESY NMR studies. Thus, the NOE correlation between the H-5_{ax} and H-3_{ax} and the small coupling constant between the β H-2 and H-3 are indicative of the $^4C_1$ chair conformation and the α equatorial disposition of the hydroxy group. This intermediate may be incorporated into the stereoselective synthesis of (+)-desoxoprosophylline (**1**), according to already published synthetic routes [1, 24].

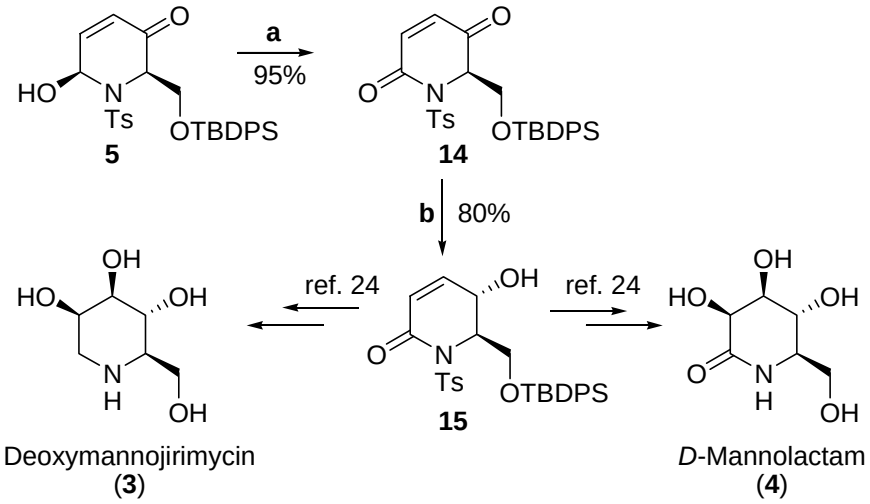
Finally, oxidation of dihydropyridone **5** with Jones reagent produced in almost quantitative yield the corresponding α,β-unsaturated-γ-keto-δ-lactam **14** (Scheme 3). The latter was diastereoselectively reduced under modified Luche conditions ($NaBH_4$ and $CeCl_3$) to 5,6-dihydropyridin-2-one **15**. This product is the key substrate for the syntheses of deoxymannojirimycin (**3**) and D-mannolactam (**4**), according to a recently published synthetic pathway [25].

Scheme 2. Synthesis of (+)-Desoxoprosophylline (**1**).



Reagents and Conditions. (a) $HC(OMe)_3$, $BF_3{\cdot}OEt_2$, 4Å molecular sieves, THF, O °C; (b) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH; (c) H_2, Pd/C, MeOH.

Scheme 3. Synthesis of Deoxymannojirimycin (**3**) and D-Mannolactam (**4**).



Reagents and conditions. (a) Jones Reagent, acetone, -10 ºC; (b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH.

Conclusions

In summary, we have demonstrated a concise synthetic route to (2*R*)-hydroxymethyl-dihydropyridone **5**, a chiral key intermediate useful in the synthesis of a variety of naturally occurring bioactive piperidine alkaloids, such as (+)-desoxoprosophylline, deoxymannojirimycin and D-mannolactam.

Experimental

General

Air- and /or moisture sensitive reactions were carried out under an argon atmosphere in flame-dried glassware. Solvents were distilled from the appropriate drying agents prior to use. All starting materials were purchased from Aldrich (analytical reagent grades) and used without further purification. 2-(tert-Butyldiphenylsilyloxy)-1-(2-furyl)ethanol (**6**, $[\alpha]_D^{22}$ +28.7, c 2.03, MeOH) was prepared according to a literature procedure [22]. All reactions were monitored by thin-layer chromatography using TLC sheets coated with silica gel 60 F_{254} (Merck); spots were visualized with UV light or/and an alcohol solution of anisaldehyde. Products were purified by flash chromatography on Merck silica gel 60 (230-400 mesh ASTM). Melting points (uncorrected): Büchi melting point apparatus. FT-IR: Nicolet Magna 750, series II. Samples were recorded as KBr pellets, unless otherwise stated. Optical rotations were measured with a Perkin-Elmer-241 polarimeter. ^{1}H-NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer, in $CDCl_3$. Chemical shifts are referenced to internal TMS. Coupling constants (*J*) are expressed in Hz. HPLC: Hewlett Packard 1100 series instrument with a variable wavelength UV detector and coupled to HP Chem-Station utilizing the manufacturer's 5.01 software package.

(S)-Ethyl-2-(tert-butyldiphenylsilanyloxy)-1-furan-2-yl benzoate (**7**). Diethyl azodicarboxylate (DEAD) (0.91 g, 5.86 mmol) was added dropwise to a solution of (*R*)-2-(*tert*-butyldiphenylsilanyloxy)-1-furan-2-yl-ethanol **6** (1.8 g, 4.91 mmol), PPh_3 (3.09 g, 11.76 mmol) and benzoic acid (1.44 g, 11.52 mmol) in dry THF (15 mL). After the mixture was stirred for 1.5 h, the solvent was evaporated. The residue was diluted with CH_2Cl_2 (150 mL) and washed with sat. aq. $NaHCO_3$ (60 mL), H_2O (80 mL) and brine. The organic phase was separated and dried over $MgSO_4$, the solvent evaporated and the residue chromatographed (hexane/EtOAc 95:5, R_f = 0.70) yielding 1.73 g (75%) of compound **7** as a colorless oil. $[\alpha]_D^{22}$ −5.7 (c 1.00, EtOAc); ^{1}H-NMR δ: 1.42 (s, 9H, C-CH_3), 4.53 (dd, *J* = 10.7, 4.8, 1H, CH_2), 4.65 (dd, *J* = 10.7, 4.8, 1H, CH_2), 6.78 (dd, *J* = 7.2, 4.9, 1H, CH), 6.88 (d, *J* = 6.8, 1H, H-3), 7.70-8.10 (m, 15H, Ph-H, H-4, H-5), 8.50 (d, *J* = 6.8, 2H, Ph-H); Anal. Calcd. for $C_{29}H_{30}O_4Si$ (470.63) C, 74.01; H, 6.43. Found: C, 74.19; H, 6.30.

(S)-2-(tert-Butyldiphenylsilanyloxy)-1-furan-2-yl-ethanol (**8**). Aqueous NaOH (10%, 0.5 mL) was added dropwise to a solution of compound **7** (1.2 g, 2.55 mmol) in MeOH (100 mL) and the reaction was run at r.t. for 3 h. The resulting mixture was quenched with sat. aq. NH_4Cl (3 mL) and extracted with EtOAc (2×150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 95:5, R_f = 0.27) gave 0.75 g (80%) of the title compound **8** as a colorless oil. $[\alpha]_D^{22}$ –4.2 (c 1.03, EtOAc); IR (neat): $\tilde{\nu}$ = 3350 (OH), 740, 1020 (furan) cm^{-1}; ^{1}H-NMR δ: 1.07 (s, 9H, C-CH_3), 3.95 (d, *J* = 1.4, 2H, CH_2), 4.83 (m, 1H, CH), 6.27 (d, *J* = 3.2, 1H, H-3), 6.3 (dd, *J* = 5.0, 1.8, 1H, H-4), 7.3-7.6 (m, 11H, Ph-H, H-5); Anal. Calcd. for $C_{22}H_{26}O_3Si$ (366.53): C, 72.09; H, 7.15. Found: C, 72.31; H, 7.02.

(R)-(2-Azido-2-furan-2-yl-ethoxy)-tert-butyldiphenylsilane (**9**). To an ice-cold solution of (2*S*)-2-furyl glycol **8** (0.4 g, 1.09 mmol) and diphenylphosphoryl azide (0.23 mL, 1.09 mmol) in dry toluene (3 mL) was added DBU (0.16 mL, 1.09 mmol) in small portions and the resulting mixture stirred for 2 h at 0 °C. The mixture was allowed to reach the room temperature, stirred for an additional 20 h and then washed successively with H_2O (2×3 mL) and 5% HCl (2 mL), dried over $MgSO_4$ and the organic layer concentrated under reduced pressure. Purification by silica gel chromatography (hexane/EtOAc 95:5, R_f = 0.87) afforded 0.33 g (78%) of azide **9** as colorless oil. $[\alpha]_D^{22}$ +50.8 (c 1.01, EtOAc); IR (neat): $\tilde{\nu}$ = 2110 (N_3), 742, 1020 (furan) cm^{-1}; ^{1}H-NMR δ: 1.10 (s, 9H, C-CH_3), 4.01 (d, *J* = 6.7, 2H, CH_2), 4.60 (t, *J* = 5.5, 1H, CH), 6.37 (d, *J* = 1.8, 2H, H-3, H-4), 7.45 (m, 7H, H-5, Ph-H), 7.70 (m, 4H, Ph-H); Anal. Calcd. for $C_{22}H_{25}N_3O_2Si$ (391.54): C, 67.49; H, 6.44; N, 10.73. Found: C, 67.27; H, 6.52; N, 10.59.

(R)-N-[2-(tert-Butyldiphenylsilyloxy)-1-furan-2-yl-ethyl]-4-methylbenzenesulfonamide (**10**). Azide **9** (0.4 g, 1.02 mmol) was dissolved in EtOAc (10 mL) and hydrogenated over 10% Pd/C (0.04 g) under 1 bar pressure for 40 min. The reaction mixture was filtered over Celite® and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (3 mL) and Et_3N (0.2 mL, 1.5 mmol) was added. The resulting solution was cooled to 0 °C and p-TsCl (0.28 g, 1.5 mmol) was added portionwise under stirring. The reaction mixture was allowed to reach r.t., stirred for an additional 3 h. and then extracted successively with sat. aq. $NaHCO_3$ (2 mL) and brine, dried over $MgSO_4$ and concentrated to dryness. The crude product was chromatographed (hexane/EtOAc 4:1, R_f = 0.4) yielding 0.5 g (94%) of the desired product **10** in pure crystalline form. M.p. 101-103 °C; $[\alpha]_D^{22}$ +5.5 (c 1.01, EtOAc); IR (neat): $\tilde{\nu}$ = 3285

(N-H), 740, 1030 (furan), cm^{-1}; ^{1}H-NMRδ: 0.99 (s, 9H, C-CH_3), 2.41 (s, 3H, PhCH_3), 3.72 (dd, *J* = 10.1, 4.9, 1H, CH_2), 3.85 (dd, *J* = 10.1, 4.9, 1H, CH_2), 4.43 (m, 1H, CH), 5.2 (d, *J* = 7.6, 1H, NH), 6.13 (d, *J* = 3.11, 1H, H-3), 6.24 (dd, *J* = 3.1, 1.9, 1H, H-4), 7.20-7.52 (m, 13H, Ph-H, H-5), 7.22 (d, *J* = 8.3, 1H), 7.66 (d, *J* = 8.0, 2H, Ph-H); Anal. Calcd. for $C_{29}H_{33}NO_4SSi$ (519.73): C, 67.02; H, 6.40; N, 2.70. Found: C, 66.78; H, 6.30; N, 2.81.

(2R,6S)-2-(tert-Butyldiphenylsilyloxyphenyl)-6-hydroxy-1-(toluene-4-sulfonyl)-1,6-dihydropyridin-3-(2H)-one (**5**). To a stirred solution of *N*-tosylfurfurylamine **10** (0.1 g, 0.19 mmol) in anhydrous CH_2Cl_2 (1 mL), *m*-chloroperbenzoic acid (70%, 0.08 g, 0.33 mmol) was added in small portions. The reaction was run at r.t. for 4 h, then washed successively with 20% aq KI (1 mL), 30% $Na_2S_2O_3$ (2 mL), sat. aq. $NaHCO_3$ (2 mL), H_2O (3 mL) and brine. Concentration under reduced pressure gave a yellowish solid, which was purified by flash chromatography (hexane/EtOAc 4:1, R_f = 0.28) providing 0.09 g (88%) of the title compound **5** as a pale white solid. A small sample was crystallized from an Et_2O/hexane mixture as off white needles. M.p. 97-99 °C; $[\alpha]_D^{22}$ –25.5 (c 1.00, MeOH); IR (neat): $\tilde{\nu}$ = 3397 (OH), 1692 (C=O), 1595 (C=C) cm^{-1}; ^{1}H-NMR δ: 0.95 (s, 9H, C-CH_3), 2.45 (s, 3H, PhCH_3), 3.60 (dd, *J* = 10.7, 2.4, 1H, CH_2), 3.90 (dd, *J* =10.7, 2.4, 1H, CH_2), 4.55 (m, 1H, H-2), 4.96 (d, *J* = 11.5, 1H, OH), 6.10 (m, 1H, H-6), 6.22 (d, *J* = 10.4, 1H, H-4), 7.08 (dd, *J* = 10.4, 4.8, 1H, H-5), 7.3-7.5 (m, 12H, Ph-H), 7.79 (d, *J* = 8.0, 2H, Ph-H); Anal. Calcd. for $C_{29}H_{33}NO_5SSi$ (535.73): C, 65.02; H, 6.21; N, 2.61. Found: C, 65.17; H, 6.28; N, 2.68.

(2R,6S)-2-(tert-Butyldiphenylsilyloxyphenyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,6-dihydropyridin-3-(2H)-one (**11**). $BF_3{\cdot}Et_2O$ (0.23 mL) was added to an ice-cold solution of pyridone **5** (0.5 g, 0.93 mmol), trimethyl orthoformate (0.3 mL, 2.75 mmol) and 4Å molecular sieves (0.35 g) in dry THF (7 mL). The reaction mixture was stirred for 3 h at 0 °C, quenched with H_2O (5 mL) and extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a yellowish solid which was chromatographed (hexane/EtOAc 4:1, R_f = 0.32) to furnish 0.45 g (88%) of desired product **11** as colorless fine needles. M.p. 84-86 °C; $[\alpha]_D^{22}$ –45 (c 1.02, EtOAc); IR (neat): $\tilde{\nu}$ = 1694 (C=O), 1596 (C=C) cm^{-1}; ^{1}H-NMR δ: 1.07 (s, 9H, C-CH_3), 2.39 (s, 3H, PhCH_3), 3.54 (s, 3H, CH_3), 3.97 (dd, *J* = 10.2, 6.6, 1H, CH_2), 4.07 (dd, *J* = 10.2, 6.6, 1H, CH_2), 4.47 (t, *J* = 6.9, 1H, H-2), 5.51 (d, *J* = 4.3, 1H, H-6), 5.74 (d, *J* = 10.36, 1H, H-4), 6.68 (dd, *J* = 10.3, 4.4, 1H, H-5), 7.24 (d, *J* = 7.4, 2H, Ph-H), 7.44 (m, 6H, Ph-H), 7.55 (d, *J* = 8.2, 2H, Ph-H), 7.67 d, *J* = 7.4, 4H, Ph-H); Anal. Calcd. for $C_{30}H_{35}NO_5SSi$ (549.75): C, 65.54; H, 6.42; N, 2.55. Found: C, 65.69; H, 6.52; N, 2.44.

(2R,3S,6S)-2-(tert-Butyldiphenylsilyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridin-3-ol (**12**). $NaBH_4$ (23.5 mg, 0.62 mmol) was added portionwise to a stirred solution of compound **11** (0.1 g, 0.18 mmol) and $CeCl_3{\cdot}7H_2O$ (33.1 mg, 0.09 mmol) in MeOH (2 mL) at –30 °C. After 40 min of stirring at that temperature, the reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and extracted with Et_2O (2×10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and chromatographed (hexane/EtOAc 4:1, R_f = 0.3) to afford 90 mg (88%) of **12** as a colorless oil, which crystallized in Et_2O/hexane as colorless fine needles. M.p. 106-107 °C; $[\alpha]_D^{22}$ −32.5 (c 0.98, EtOAc); IR (neat): $\tilde{\nu}$ = 3460 (OH), 1650 (C=C) cm^{-1}; ^{1}H-NMR δ: 1.05 (s, 9H, C-CH_3), 2.42 (s,

3H, $PhCH_3$), 3.31 (s, 3H, CH_3), 3.77 (dd, *J* = 10.6, 4.2, 1H, CH_2), 3.95 (m, 1H, H-3), 4.17 (d, *J* = 6.85, 1H, OH), 4.2 (m, 1H, H-2), 4.4 (t, *J* = 10.3, 1H, CH_2), 5.24 (m, 1H, H-6), 5.69 (m, 1H, H-5), 5.84 (m, 1H, H-4), 7.25 (t, *J* = 9.01, 2H, Ph-H), 7.4-7.5 (m, 6H, Ph-H), 7.6-7.7 (m, 6H, Ph-H); Anal. Calcd. for $C_{30}H_{37}NO_5SSi$ (551.8): C, 65.30; H, 6.76; N, 2.54. Found: C, 65.55; H, 6.90; N, 2.63.

2-(tert-Butyldiphenylsilanyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-piperidin-3-ol (**13**). Allylic alcohol **12** (0.52 g, 1 mmol) was dissolved in MeOH (15 mL) and hydrogenated over 10% Pd/C (52 mg) under 1 bar pressure for 2 h. The mixture was filtered over Celite®, evaporated and partitioned between EtOAc and water. The aqueous layer was backwashed with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The yellowish slurry was chromatographed (hexane/EtOAc 4:1, R_f = 0.29) to give 90 mg (90%) of compound **13** as an off-white solid. M.p. 98-100 °C; $[\alpha]_D^{22}$ −15.5 (c 1.02, EtOAc); IR (neat): $\tilde{\nu}$ = 3500 (OH) cm^{-1}; ^{1}H-NMR δ: 1.07 (s, 9H, C-CH_3), 1.65 (m, 2H, H-4), 1.9 (m, 2H, H-5), 2.4 (s, 3H, $PhCH_3$), 3.1 (s, 3H, CH_3), 3.44 (m, 1H, H-3), 3.66 (m, 1H, CH_2), 3.88 (dd, *J* = 10.2, 4.1, 1H, H-2), 4.35 (d, *J* = 6.26, 1H, OH), 4.5 (t, *J* = 10.4, 1H, CH_2), 5.01 (m, 1H, H-6), 7.27 (t, *J* = 8.15, 2H, Ph-H), 7.3-7.5 (m, 6H, Ph-H), 7.6-7.7 (m, 6H, Ph-H); Anal. Calcd. for $C_{30}H_{39}NO_5SSi$ (553.8): C, 65.07; H, 7.10; N, 2.53. Found: C, 65.31; H, 7.23; N, 2.42.

(6R)-6-(tert-Butyldiphenylsilyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,6-dihydropyridine-2,5-dione (**14**). To an ice cold solution of compound **5** (0.1 g, 0.188 mmol) in acetone (1.3 mL) at –10 °C, was added dropwise Jones reagent (0.1 mL). After being stirred for 20 min, the solid inorganic by products were eliminated by decantation and the liquid layer was concentrated to a residue that was partitioned in EtOAc (4 mL) and H_2O (2 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated. The residue was crystallized from cold Et_2O/hexane to afford 95 mg (95%) of compound **14** as an off-white solid. M.p. 196-198 °C; R_f = 0.31 (hexane/EtOAc 1:4); $[\alpha]_D^{22}$ −10.7 (c 1.00, EtOAc); IR (neat): $\tilde{\nu}$ = 1725 (C=O), 1692 (N-C=O) cm^{-1}; ^{1}H-NMR δ: 0.92 (s, 9H, C-CH_3), 2.44 (s, 3H, $PhCH_3$), 4.11 (dd, *J* = 10.6, 1.6, 1H, CH_2), 4.42 (dd, *J* =10.6, 1.6, 1H, CH_2), 5.02 (s, 1H, H-6), 6.72 (d, *J* = 10.1, 1H, H-3), 6.8 (d, *J* = 10.1, 1H, H-4), 7.27 (d, *J* = 8.1, 2H, Ph-H), 7.3-7.55 (m, 10H, Ph-H), 7.94 (d, *J* = 8.3, 2H, Ph-H); Anal. Calcd. for $C_{29}H_{31}NO_5SSi$ (533.7): C, 65.26; H, 5.85; N, 2.62. Found. C, 65.01; H, 5.98; N, 2.49.

(5S,6R)-2-(tert-Butyldiphenylsilyloxymethyl)-5-hydroxy-1-(toluene-4-sulfonyl)-5,6-dihydropyridin-2-one (**15**). $NaBH_4$ (24 mg, 0.64 mmol) was added portionwise to a stirred solution of compound **14** (0.1 g, 0.187 mmol) and $CeCl_3 \cdot 7H_2O$ (34 mg, 0.092 mmol) in MeOH (2 mL) at –30 °C. After 40 min of stirring at that temperature, the reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and extracted with Et_2O (2×10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and chromatographed (hexane/EtOAc 4:1, R_f = 0.4) to afford compound **15** (80 mg, 80%) as a pale white solid. M.p. 150-152 °C; $[\alpha]_D^{22}$ −2.7 (c 1.02, EtOAc); IR (neat): $\tilde{\nu}$ = 1450 (C=O), 1670 (N-C=O) cm^{-1}; ^{1}H-NMR δ: 0.92 (s, 9H, C-CH_3), 2.44 (s, 3H, $PhCH_3$), 3.82 (dd, *J* = 10.6, 4.2, 1H, CH_2), 4.02 (dd, *J* = 10.6, 4.2, 1H, CH_2), 4.17 (d, *J* = 6.85, 1H, OH), 5.04 (m, 1H, H-5), 5.04 (m, 1H, H-5), 5.07 (m, 1H, H-6), 5.60 (dd, *J* = 10.0, 4.2, 1H, H-4), 7.01 (dt, *J* = 10.2, 1.7, 1H, H-3), 7.2 (d, *J* = 7.2, 2H, Ph-H), 7.40-

7.52 (m, 6H, Ph-H), 7.60 (dd, *J* = 7.5, 1.5, 2H, Ph-H), 7.7 (d, *J* = 8.4, 4H, Ph-H); Anal. Calcd. for $C_{29}H_{31}NO_5SSi$ (533.7): C, 65.26; H, 5.85; N, 2.62. Found: C, 65.09; H, 5.71; N, 2.72.

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