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Asymmetric synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid δ-lactam derivatives

Sofia D. Koulocheri,[a] Prokopios Magiatis,[b] Alexios-Leandros Skaltsounis[b] and Serkos A. Haroutounian[a,*]

[a]*Chemistry Laboratory, Agricultural University of Athens, Iera odos 75, Athens 11855, Greece*
[b]*Department of Pharmacy, University of Athens, Panepistimiopolis Zografou, Athens 15771, Greece*

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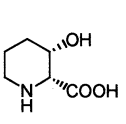
Abstract—A practical synthetic scheme that incorporates an amide functionality into the rigid framework of (2*S*,3*R*)-3-hydroxypipecolic acid to produce novel hydroxylated δ-lactam derivatives is reported. The reaction sequence includes the transformation of chiral furanylazide to a 2*S*-hydroxymethyldihydro pyridone, which was reduced diasteroselectively, protected and oxidized to two corresponding δ-lactam derivatives. Asymmetric dihydroxylation and oxidation of the latter compounds afforded two chiral (2*R*,3*S*)-3-hydroxypipecolic acid δ-lactam derivatives.

1. Introduction

3-Hydroxypipecolic acid derivatives constitute the common structural sub-units of a wide variety of naturally occurring alkaloids[1] and drugs.[2] Compounds with this unnatural amino acid scaffold are known to possess a broad range of significant pharmacological properties[3] and medicinal chemists often incorporate their structural motif in the design and synthesis of novel biologically active molecules. Over the past years, the 3-hydroxypipecolic acid framework has been incorporated in the preparation of compounds with diverse activities, such as immunosupressants,[4] enzyme inhibitors,[5] NMDA antagonists,[6] anticancer[7] and anti-HIV[8] agents. Furthermore, there are many current reports concerning the use this core structure, as conformationally constrained α-amino β-hydroxy acid, in the synthesis of peptidomimetics.[9] Thus, the development of synthetic strategies, which would provide enantioselective access to novel derivatives of 3-hydroxypipecolic acid, is highly desired and the subject of significant research activity.[10]

Surprisingly, among the four possible isomers of 3-hydroxypipecolic acid, the synthesis of the (2*R*,3*S*)-enantiomer (**1**) is less documented, since there are only limited examples of its synthesis and derivatization.[11] This has captured our research interest, which was further stimulated by the potential of these molecules to induce a secondary structure in a short sequence. Example of such a hybrid design that amalgamates in a single molecule the structural frameworks of a sugar and an amino acid, two fundamental building blocks used in nature, has already been represented by a special class of compounds called sugar amino acids (Saa).[12]

In this report we present the incorporation of an amide functional group into the rigid heterocyclic framework of (2*S*,3*R*)-3-hydroxypipecolic acid to produce novel hydroxylated δ-lactam derivatives. The latter belong to a class of compounds which recently has received considerable attention[13] due to their significant biological properties, such as anti-inflammatory activity[14] and inhibition of glucosidases[15] or cancer cell metastasis.[16] To date, sodium D-glucaro-δ-lactam (ND-2001, **2**) a derivative of (2*S*,3*S*)-3-hydroxypipecolic acid, is the only example in the literature of a compound with such a structural framework.[17] This compound is a potent inhibitor of β-glucurodinase, with 98.5% inhibition at 0.1 mM and also exhibits significant antimetastatic activity on a pulmonary model of mouse melanoma B16, with 91.8% metastatic inhibition at 10 μg/mL.[18]



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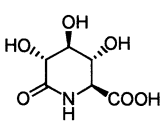

ND-2001, **2**

2. Results and discussion

Our synthetic approach relies on chiral furanylazide **3**, which provides the stereogenic center for the enantioselective elaboration of the piperidine ring. This compound was efficiently prepared in high enantiomeric excess from the

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* Corresponding author. Tel.: +30-10-5294247; fax: +30-10-5294265; e-mail: sehar@aua.gr

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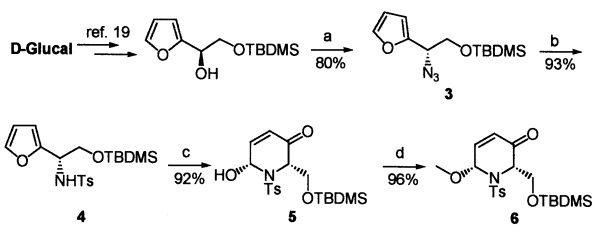
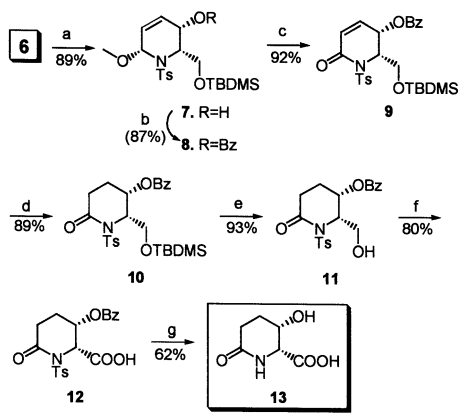


Scheme 1. (a) DPPA, DBU, toluene, 0°C; (b) (i) H_2, Pd/C, MeOH; (ii) TsCl, Et_3N, CH_2Cl_2; (c) *m*-CPBA, CH_2,Cl_2; (d) $HC(OMe)_3$, $BF_3{\cdot}OEt_3$, 4 Å molecular sieves, THF, 0°C.

readily available D-glucal, according to a recently reported method.[19] Subsequent hydrogenation and oxidative cyclization furnished the 2*S*-hydroxymethyl-dihydropyridone **5**, which was further protected to compound **6**, the key intermediate for the construction of the target 3-hydroxy-pipecolic acid δ-lactam derivatives (Scheme 1).

Reduction of intermediate **6** under modified Luche conditions[20] resulted in the formation of alcohol **7** as a single diastereomer, which has the 3-hydroxy group with an equatorial disposition. Benzoylation of the hydroxy group and subsequent oxidation afforded smoothly the α,β-unsaturated-δ-lactam **9**, which subsequently was hydrogenated to produce the saturated δ-lactam **10**. At this stage, it is necessary to point out that it is essential to use the protected substrate, since catalytic hydrogenation of the unprotected 5-hydroxy-δ-lactam led to the exclusive formation of the corresponding γ-lactone, via a ring opening and in situ intramolecular acylation mechanism. The silyl-protecting group was efficiently cleaved by treatment with TBAF, while subsequent attempt to oxidize the hydroxymethyl moiety using Jones reagent proved troublesome, since it led to the formation of a variety of unidentified products. Thus, the oxidation was performed using ruthenium tetroxide (prepared in situ from ruthenium trichloride and sodium periodate), while cleavage of the protecting groups provided the target (2*R*,3*S*)-3-hydroxy-pipecolic acid δ-lactam derivative **13** (Scheme 2).



Scheme 2. (a) $NaBH_4$, $CeCl_3{\cdot}H_2O$, MeOH, −30°C; (b) BzCl, Et_3N, CH_2Cl_2; (c) *m*-CPBA, $BF_3{\cdot}Et_2O$, THF; (d) H_2, Pd/C, MeOH; (e) TBAF, THF; (f) $RuCl_3$, $NaIO_4$, $H_2O/CCl_4/CH_3CN$; (g) Na, naphthalene, THF.

Accordingly, the synthesis of the polyhydroxylated 2*R*-pipecolic acid δ-lactam derivative started with the benzylation of compound **7**, which by oxidation was transformed to the corresponding α,β-unsaturated-δ-lactam

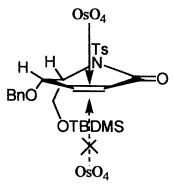


Figure 1. Spatial view of the osmium tetroxide attack on compound **15**.

15. The next step of the synthetic route called for the diastereoselective dihydroxylation of the double bond. In that regard, treatment of **15** with OsO_4 and 4-methyl-morpholine *N*-oxide afforded the dihydroxy piperidine derivative **16** as a single diastereomer. The high diastereoselectivity of this reaction may be rationalized considering that the addition occurred from the less sterically hindered *si* face of the molecule, since the opposite side (*re*) is effectively shielded by the sterically demanding *tert*-butyl-dimethyl-silyl group (Fig. 1). The diastereomeric purity of the product was revealed by HPLC and ^1H NMR spectroscopic analyses, since no traces of any other diastereomer was detected. The *cis* configuration, including the 3-axial and 4-equatorial orientation of the hydroxy groups, was elucidated unambiguously by diagnostic coupling constants and 2D-NOESY spectroscopy of compound **16**. More specifically, the strong NOE signals between the protons of methylene group of hydroxymethyl moiety and H-3 are indicative of the axial orientation of the hydroxy group of carbon atom C-3. This assignment was reinforced by the NOE enhancement between the said hydroxy proton and H-5. On the other hand, the intense NOE signals between H-4 and the protons of methylene group of hydroxymethyl

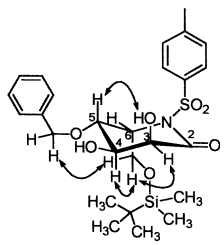
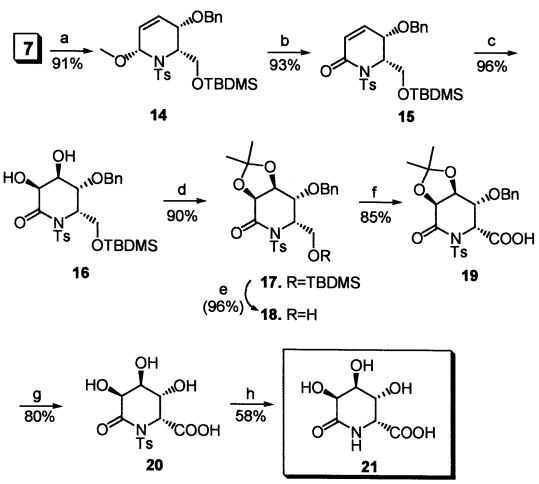


Figure 2. NOE Correlations in **16**.



Scheme 3. (a) NaH, BnBr, Bu_4NI, THF; (b) *m*-CPBA, $BF_3{\cdot}Et_2O$, THF; (c) OsO_4, NMO, *t*-BuOH/acetone (1:1); (d) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH·H_2O, aceton; (e) TBAF, THF, (f) $RuCl_3$, $NaIO_4$, $H_2O/CCl_4/CH_3CN$; (g) (i) H_2, Pd/C, EtOH; (ii) *p*-TsOH·H_2O, MeOH; (h) Na, naphthalene, THF.

moiety or the benzylic protons, proved the equatorial orientation of the hydroxy group of carbon atom C-4. Finally, the large coupling constant (10.5 Hz) observed between H-4 and H-5 is consistent with the axial orientation of H-4 reinforcing the previous assignment (Fig. 2, Scheme 3).

Acetalization of diol **16** and subsequent cleavage of the silyl-protecting group gave compound **18**, which was oxidized with ruthenium tetroxide to produce the protected pipecolic acid-δ-lactam derivative **19**. Finally, hydrogenolysis of the benzyl ether and subsequent sequential removal of the acetonide and tosyl protective groups provided the target (2*R*,3*R*,4*S*,5*S*)-trihydroxypipecolic acid δ-lactam derivative **21** in 12 steps and 20% overall yield from furanylazide **3**.

In conclusion, we have described a simple and efficient synthetic route that allows the incorporation of an amide functionality into the rigid framework of 3-hydroxy pipecolic acid to produce novel chiral hydroxylated pipecolic acid δ-lactam derivatives.

3. Experimental

3.1. General comments

^{1}H and 2D NMR spectra were recorded on Bruker DRX-400 or AC-200 spectrometers (400 and 200 MHz, respectively). IR spectra were obtained on a Nicolet Magna 750, series II spectrometer. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at ambient temperature. HPLC separations were performed using a 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. TLC was conducted on Merck glass plates coated with silica gel 60 F_{254}. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM).

All reactions (except hydrogenations) were carried out under argon atmosphere. Solvents were dried by distillation. Tetrahydrofuran was distilled from sodium-benzophenone and methylene chloride over CaH_2 immediately prior to use. Starting materials were purchased from Aldrich (analytical reagent grades) and used without further purification.

3.1.1. (*S*)-(2-Azido-2-furan-2-yl-ethoxy)-*tert*-butyl-dimethyl-silane (3). To an ice-cold solution of (2*R*)-2-furyl glycol (2.4 g, 10 mmol) and diphenylphosphorazide (2.7 mL, 12 mmol) in dry toluene (25 mL), DBU (1.8 mL, 12 mmol) was added. After stirring for 10 h at that temperature, the reaction mixture was washed successively with H_2O (2×15 mL), sat. NH_4Cl (20 mL) and the organic layer was concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/hexane 5:95, R_f 0.83) afforded azide **4** as colorless oil (2.14 g, 80%). $[\alpha]_D^{22}=-40.6$ (*c* 1.1, EtOAc); IR (neat): ν_{max} 2109 (N_3), 742, 1017 (furan) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.09 (s, 6H), 0.9 (s, 9H), 3.93 (dd, *J*=10.1, 7.0 Hz, 1H), 4.00 (dd, *J*=10.1, 4.5 Hz, 1H), 4.52 (dd, *J*=7.0, 4.5 Hz, 1H), 6.35 (m, 2H), 7.37 (s, 1H). Anal. calcd for $C_{12}H_{21}N_3O_2Si$ (267.4): C, 53.90; H, 7.92; N, 15.71. Found: C, 54.21; H, 7.84; N, 15.79.

3.1.2. (*S*)-*N*-[2-(*tert*-Butyl-dimethyl-silyloxy)-1-furan-2-yl-ethyl]-4-methyl-benzenesulfonamide (4). Azide **3** (2 g, 7.48 mmol) was dissolved in EtOAc (50 mL) and hydrogenated over 0.2 g of Pd/C (10%) 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 (20 mL) and triethylamine (1.3 mL, 9.75 mmol) was added. The resulting solution was cooled to 0°C and *p*-toluenesulfonyl chloride (1.86 g, 9.75 mmol) was added portionwise under stirring. The reaction allowed to reach rt and stirred for additional 3 h. Then, the mixture was extracted successively with $NaHCO_3$, brine and the solvent was evaporated. The resulting solid was chromatographed (EtOAc/hexane 1:4, R_f 0.4) yielding the desired product **4** as colorless fine needles (2.57 g, 87%). Mp 55–57°C (Et_2O/hexane); $[\alpha]_D^{22}=-31.1$ (*c* 1.15, EtOAc); IR (neat): ν_{max} 3293 (N–H), 741, 1019 (furan) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.07 (s, 6H), 0.80 (s, 9H), 2.39 (s, 3H), 3.69 (dd, *J*=10.1, 4.8 Hz, 1H), 3.82 (dd, *J*=10.1, 4.8 Hz 1H), 4.45 (dt, *J*=7.5, 4.8 Hz, 1H), 5.18 (d, *J*=7.5 Hz, 1H), 6.10 (d, *J*=3.1 Hz, 1H), 6.19 (dd, *J*=3.1, 1.8 Hz, 1H), 7.19 (d, *J*=1.8 Hz, 1H), 7.22 (d, *J*=8.3 Hz, 1H), 7.66 (d, *J*=8.3 Hz, 1H). Anal. calcd for $C_{19}H_{29}NO_4SSi$ (395.6): C, 57.69; H, 7.39; N, 3.54. Found: C, 57.41; H, 7.22; N, 3.71.

3.1.3. (2*S*,6*R*)-2-(*tert*-Butyl-dimethyl-silyloxymethyl)-6-hydroxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (5). To a stirred solution of *N*-tosylfurfurylamine **4** (2.31 g, 5.84 mmol) in anhydrous CH_2Cl_2 (30 mL), *m*-chloroperbenzoic acid 70% (2.08 g, 8.8 mmol) was added. The reaction mixture was stirred at rt for 4 h, then washed successively with 20% KI, 30% $Na_2S_2O_3$, sat. $NaHCO_3$, water, brine and concentrated under reduced pressure to a yellowish solid. Purification by flash chromatography (EtOAc/hexane 1:4, R_f 0.33) gave the title compound as a pale white solid (2.21 g, 92%). A small sample was recrystallized from Et_2O/hexane mixture as off white needles. Mp 101–103°C; $[\alpha]_D^{22}=-26.7$ (*c* 0.84, EtOAc); IR (neat): ν_{max} 3362 (OH), 1698 (C=O), 1639 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.01 (s, 6H), 0.72 (s, 9H), 2.37 (s, 3H), 3.54 (d, *J*=10.6 Hz, 1H), 3.89 (dd, *J*=10.6 Hz, 1H), 4.48 (s, 1H), 4.92 (d, *J*=11.4 Hz, 1H), 5.94 (dd, *J*=11.4, 5.1 Hz, 1H), 6.05 (d, *J*=10.5 Hz, 1H), 6.92 (dd, *J*=10.5, 5.1 Hz, 1H), 7.25 (d, *J*=8.5 Hz, 2H), 7.75 (d, *J*=8.5 Hz, 2H). Anal. calcd for $C_{19}H_{29}NO_5SSi$ (411.6): C, 55.44; H, 7.10; N, 3.40. Found: C, 55.68; H, 7.35; N, 3.51.

3.1.4. (2*S*,6*R*)-2-(*tert*-Butyl-dimethyl-silyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (6). To an ice-cold solution of azapyranone **5** (1.53 g, 3.72 mmol), trimethyl orthoformate (0.8 mL, 7.44 mmol) and 4 Å molecular sieves (0.35 g) in dry THF (25 mL), $BF_3{\cdot}Et_2O$ (0.7 mL) was added. The reaction mixture was stirred for 3 h at 0°C, then quenched with water and extracted with Et_2O (2×30 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 (EtOAc/hexane 1:4, R_f 0.35) to furnish the desired product **6** (1.49 g, 94%) as

colorless fine needles. mp 68–70°C (Et_2O/hexane); $[\alpha]_D^{22}$=+106 (*c* 0.51, EtOAc); IR (neat): ν_{max} 1695 (C=O), 1637 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.05 (s, 6H), 0.89 (s, 9H), 2.40 (s, 3H), 3.58 (s, 3H), 3.94 (dd, *J*=10.1, 7.3 Hz 1H), 4.00 (dd, *J*=10.1, 7.5 Hz, 1H), 4.39 (t, *J*=7.3 Hz, 1H), 5.55 (dd, *J*=4.4, 0.9 Hz, 1H), 5.78 (d, *J*=10.1 Hz, 1H), 6.74 (dd, *J*=10.1, 4.4 Hz, 1H), 7.25 (d, *J*=8.3 Hz, 2H), 7.59 (d, *J*=8.3 Hz, 2H). Anal. calcd for $C_{20}H_{31}NO_5SSi$ (425.6): C, 56.44; H, 7.34; N, 3.29. Found: C, 56.55; H, 7.11; N, 3.34.

3.1.5. (2*S*,6*R*)-2-(*tert*-Butyl-dimethyl-silyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridin-3-ol (7). To a stirred solution of compound **6** (0.76 g, 1.80 mmol) and $CeCl_3 \cdot 7H_2O$ (0.33 g, 0.90 mmol) in methanol (20 mL) at −30°C, $NaBH_4$ (0.24 g, 6.23 mmol) was added portionwise. After 40 min of stirring at that temperature, the reaction was quenched with sat. NH_4Cl (15 mL) and extracted with EtOAc (3×20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and chromatographed (EtOAc/hexane 1:4, R_f 0.3) to afford **7** as colorless oil (0.68 g, 89%). $[\alpha]_D^{22}$=+60 (*c* 0.9, EtOAc); IR (neat): ν_{max} 3445 (OH), 1650 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.05 (s, 6H), 0.84 (s, 9H), 2.40 (s, 3H), 3.45 (s, 3H), 3.66 (dd, *J*=10.5, 3.9 Hz), 3.82 (m, 1H), 4.04 (dt, *J*=10.1, 5.3 Hz, 1H), 4.3 (m, 2H), 5.24 (s, 1H), 5.66 (dt, *J*=10.3, 2.2 Hz, 1H), 5.77 (d, *J*=10.3 Hz, 1H), 7.25 (d, *J*=8.3 Hz, 2H), 7.66 (d, *J*=8.3 Hz, 2H). Anal. calcd for $C_{20}H_{33}NO_5SSi$ (427.6): C, 56.17; H, 7.78; N, 3.28. Found: C, 56.35; H, 7.89; N, 3.11.

3.1.6. (2*S*,3*S*)-Benzoic acid 2-(*tert*-butyl-dimethyl-silyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridin-3-yl ester (8). To a stirred ice-cold solution of **7** (0.65 g, 1.52 mmol), and triethylamine (0.24 mL, 1.82 mmol) in dry CH_2Cl_2 (10 mL), BzCl (0.21 mL, 1.82 mmol) was added dropwise under stirring. The reaction allowed to reach the rt and stirred for additional 1 h. The mixture was extracted successively with sat. NH_4Cl (10 mL), brine and the solvent was evaporated. The resulting solid was chromatographed (EtOAc/hexane 1:4, R_f 0.48) to yield the desired product **8** as colorless oil (0.78 g, 87%). $[\alpha]_D^{22}$=+72.3 (*c* 0.7, EtOAc); IR (neat): ν_{max} 1645 (C=C), 1710 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.05 (s, 6H), 0.85 (s, 9H), 2.41 (s, 3H), 3.45 (s, 3H), 4.08 (m, 2H), 4.35 (m, 1H), 4.84 (m, 1H), 5.24 (s, 1H), 5.75 (dt, *J*=10.0, 2.1 Hz, 1H), 5.80 (d, *J*=10.0 Hz, 1H), 7.18 (d, *J*=8.1 Hz, 2H), 7.37 (m, 2H), 7.46 (m, 1H), 7.60 (d, *J*=8.1 Hz, 2H), 7.92 (m, 2H). Anal. calcd for $C_{27}H_{37}NO_6SSi$ (531.7): C, 60.99; H, 7.01; N, 2.63. Found: C, 61.24; H, 6.93; N, 2.51.

3.1.7. (2*S*,3*S*)-Benzoic acid 2-(*tert*-butyl-dimethyl-silyloxymethyl)-6-oxo-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridin-3-yl ester (9). To a solution of **5** (0.75 g, 1.41 mmol) and 4 Å molecular sieves (0.54 g) in dry CH_2Cl_2 (7 mL) at −15°C, *m*-chloroperbenzoic acid 70% (0.4 g, 1.65 mmol) dissolved in dry CH_2Cl_2 (3 mL) and freshly distilled $BF_3 \cdot Et_2O$ (0.2 mL, 1.65 mmol) were added. The reaction was allowed to proceed the rt and stirred for 2 h. Then the reaction was quenched with sat. $NaHCO_3$ (2 mL) and the resulting mixture was filtered through a pad of celite. The filtrate was poured into 15 mL of water and extracted with Et_2O (2×20 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 (EtOAc/hexane 1:4, R_f 0.50) to furnish the desired product **9** as an off-white solid (0.67 g, 92%); mp 77–78°C (Et_2O/hexane); $[\alpha]_D^{22}$=+56.8 (*c* 0.7, EtOAc); IR (neat): ν_{max} 1645 (C=C), 1676 (N–C=O), 1710 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.05 (s, 6H), 0.82 (s, 9H), 2.38 (s, 3H), 4.15 (m, 2H), 4.32 (m, 1H), 4.78 (m, 1H), 5.68 (dd, *J*=10.2, 2.4 Hz, 1H), 6.69 (dt, *J*=10.2, 1.7 Hz, 1H), 7.25 (d, *J*=8.2 Hz, 2H), 7.35 (m, 2H), 7.46 (m, 1H), 7.65 (d, *J*=8.2 Hz, 2H), 7.92 (m, 2H). Anal. calcd for $C_{26}H_{33}NO_6SSi$ (515.7): C, 60.55; H, 6.45; N, 2.72. Found: C, 60.71; H, 6.33; N, 2.57.

3.1.8. (2*S*,3*S*)-Benzoic acid 2-(*tert*-butyl-dimethyl-silyloxymethyl)-6-oxo-1-(toluene-4-sulfonyl)-piperidin-3-yl ester (10). Olefin **9** (0.52 g, 1 mmol) was dissolved in MeOH (15 mL) and hydrogenated over 10% Pd/C (51 mg) under 1 bar pressure for 2 h. The mixture was filtered through celite and partitioned between EtOAc and water. The aqueous layer was washed with EtOAc and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The yellowish slurry was chromatographed (EtOAc/hexane 1:4, R_f 0.52) to give compound **10** (0.46 g, 89%) as an off-white solid. Mp 85–86°C (Et_2O/hexane); $[\alpha]_D^{22}$=+63.6 (*c* 0.3, EtOAc); IR (neat): ν_{max} 1692 (N–C=O), 1725 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.05 (s, 6H), 0.83 (s, 9H), 1.71 (dd, *J*=12.8, 2.41 Hz, 1H), 1.90 (m, 1H), 2.39 (s, 3H), 2.42 (m, 1H), 2.55 (dd, *J*=12.0, 1.7 Hz, 1H), 4.21 (m, 2H), 4.56 (m, 1H), 4.71 (m, 1H), 7.18 (d, *J*=8.0 Hz, 2H), 7.40–7.47 (m, 3H), 7.68 (d, *J*=8.0 Hz, 2H), 7.89 (m, 2H). Anal. calcd for $C_{26}H_{35}NO_6SSi$ (517.7): C, 60.32; H, 6.81; N, 2.71. Found: C, 60.50; H, 6.85; N, 2.58.

3.1.9. (2*S*,3*S*)-Benzoic acid 2-hydroxymethyl-6-oxo-1-(toluene-4-sulfonyl)-piperidin-3-yl ester (11). To a solution of **10** (0.45 g, 0.87 mmol) in THF (7 mL), TBAF (1.0 M solution in THF, 1.25 mL) was added. The mixture was stirred for 2 h and the solvent was evaporated under reduced pressure. The yellowish slurry was purified by chromatography (EtOAc/hexane 1:4, R_f 0.21) to give alcohol **11** (0.33 g, 93%) as a colorless oil. $[\alpha]_D^{22}$=+37.5 (*c* 0.3, EtOAc); IR (neat): ν_{max} 3444 (OH), 1690 (N–C=O), 1720 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.69 (m, 1H), 1.92 (m, 1H), 2.44 (s, 3H), 2.44 (m, 1H), 2.59 (m, 1H), 3.80 (m, 1H), 3.98 (m, 1H), 4.02 (m, 1H), 4.95 (m, 1H), 7.18 (d, *J*=8.3 Hz, 2H), 7.40–7.47 (m, 3H), 7.59 (d, *J*=8.3 Hz, 2H), 7.89 (m, 2H). Anal. calcd for $C_{20}H_{21}NO_6S$ (403.5): C, 59.54; H, 5.25; N, 3.47. Found: C, 59.41; H, 5.32; N, 3.64.

3.1.10. (2*R*,3*S*)-3-Benzoyloxy-6-oxo-1-(toluene-4-sulfonyl)-piperidine-2-carboxylic acid (12). To a stirred solution of alkene **11** (0.35 g, 0.87 mmol) in $H_2O/CCl_4/CH_3CN$ (1.5:1:1 v/v, 6 mL), $NaIO_4$ (0.74 g, 3.49 mmol) and a catalytic amount of $RuCl_3$ (3.8 mg, 0.015 mmol) were added. The mixture was stirred for 2 h, quenched with propan-2-ol and filtered through a celite pad. The filtrate was evaporated to a yellowish slurry which was purified by chromatography ($CHCl_3$/MeOH 3:2 R_f 0.45) yielding **12** (0.29 g, 80%) as a foamy solid. $[\alpha]_D^{22}$=+122.9 (*c* 0.3, $CHCl_3$); IR (neat): ν_{max} 1660 (N–C=O), 1740, 1720

(C═O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.75 (m, 1H), 1.87 (m, 1H), 2.42 (s, 3H), 2.44 (m, 1H), 2.56 (m, 1H), 3.95 (m, 1H), 4.68 (m, 1H), 7.18 (d, J=8.3 Hz, 2H), 7.40–7.47 (m, 3H), 7.59 (d, J=8.3 Hz, 2H), 7.89 (m, 2H). Anal. calcd for $C_{20}H_{19}NO_7S$ (417.4): C, 57.55; H, 4.59; N, 3.36. Found: C, 57.81; H, 4.41; N, 3.42.

3.1.11. (2*R*,3*S*)-3-Hydroxy-6-oxo-piperidine-2-carboxylic acid (13). To a stirred solution of naphthalene (71 mg, 0.55 mmol) in freshly distilled THF (2.5 mL), sodium (13 mg, 0.53 mmol) was added. After 45 min of stirring at ambient temperature (dark-green color), the mixture was cooled to −78°C and a solution of compound **12** (200 mg, 0.48 mmol) in THF (2 mL) was added. The reaction mixture was stirred at that temperature for 30 min, quenched with sat. aqueous NH_4Cl (15 mL) and extracted with $CHCl_3$ (2×20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give the target molecule **13** (47 mg, 62%). An analytically pure sample was obtained as white prisms by crystallization from MeOH/Et_2O. Mp 220–225°C (decomp.); $[\alpha]_D^{22}$=+36.5 (*c* 0.3, MeOH); IR (neat): ν_{max} 3420 (OH), 1650 (N–C═O), 1735 (C═O) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ_H 1.80 (m, 2H), 2.38 (m, 2H), 3.91 (m, 1H), 4.67 (s br, 1H). Anal. calcd for $C_6H_9NO_4$ (159.1): C, 54.28; H, 5.70; N, 8.80. Found: C, 54.39; H, 5.82; N, 8.73.

3.1.12. (2*S*,3*S*,6*R*)-3-Benzyloxy-2-(*tert*-butyl-dimethyl-silyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine (14). To an ice-cold solution of compound **7** (0.94 g, 2.20 mmol) in dry THF (3.5 mL), sodium hydride (63 mg, 2.64 mmol) was added in portions under stirring. The reaction mixture was allowed to reach the rt and stirred for 30 min. Then, a catalytic amount of Bu_4NI (40 mg, 0.11 mmol) and benzyl bromide (0.37 mL, 3.31 mmol) were added. After 2 h of stirring, the reaction was quenched with sat. aq NH_4Cl (8 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to a yellowish slurry which was purified by chromatography (EtOAc/hexane 1:4, R_f 0.55) yielding **14** (1.04 g, 91%) as colorless oil. $[\alpha]_D^{22}$=+106.2 (*c* 0.3, EtOAc); ^1H NMR (400 MHz, $CDCl_3$): ^1H NMR: δ_H 0.05 (s, 6H), 1.04 (s, 9H), 2.41 (s, 3H), 3.50 (s, 3H), 3.97 (dd, J=11.1, 3.2 Hz, 1H), 4.01 (m, 1H), 4.15 (m, 2H), 4.53 (d, J=11.5 Hz, 1H), 4.60 (d, J=11.5 Hz, 1H), 5.24 (s,1H), 5.66 (dt, J=10.2, 2.2 Hz, 1H), 5.75 (d, J=10.2 Hz, 1H), 7.21 (d, J=7.9 Hz, 2H), 7.25 (d, J=8.3 Hz, 2H), 7.34 (m, 3H), 7.67 (d, J=8.3 Hz, 2H). Anal. calcd for $C_{27}H_{39}NO_5SSi$ (517.8): C, 62.63; H, 7.59; N, 2.71. Found: C, 62.48; H, 7.38; N, 2.55.

3.1.13. (5*S*,6*S*)-5-Benzyloxy-6-(*tert*-butyl-dimethyl-silyl-oxymethyl)-1-(toluene-4-sulfonyl)-5,6-dihydro-1*H*-pyridin-2-one (15). A solution of **14** (0.93 g, 1.8 mmol) and 4 Å molecular sieves (0.65 g) in dry CH_2Cl_2 (10 mL) was cooled at −15°C and a solution *m*-chloroperbenzoic acid 70% (0.48 g, 1.98 mmol) in dry CH_2Cl_2 (4 mL) and freshly distilled $BF_3{\cdot}Et_2O$ (0.25 mL, 2 mmol) were added. The reaction allowed to reach the rt and stirred for 2 h. Then the reaction was quenched with $NaHCO_3$ (2.5 mL) and the resulting mixture was filtered through a pad of celite. The filtrate was poured into 18 mL of water and extracted with Et_2O (2×20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellowish solid which was chromatographed (EtOAc/hexane 1:4, R_f 0.27) to furnish the desired product **15** (0.84 g, 93%) as colorless oil. $[\alpha]_D^{22}$=+39.3 (*c* 0.65, EtOAc); IR (neat): ν_{max} 1675 (N–C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.05 (s, 6H), 1.04 (s, 9H), 2.41 (s, 3H), 3.95 (dd, J=11.4, 3.2 Hz, 1H), 4.14 (dd, J=11.4, 3.9 Hz, 1H), 4.56 (d, J=11.5 Hz, 1H), 4.63 (d, J=11.5 Hz, 1H), 4.73 (dt, J=7.0, 2.0 Hz, 1H), 5.04 (m, 1H), 5.75 (dd, J=10.1, 2.9 Hz, 1H), 6.63 (d, J=10.1 Hz, 1H), 7.17 (dd, J=5.7, 3.5 Hz, 2H), 7.21 (d, J=8.3 Hz, 2H), 7.30 (m, 3H), 7.70 (d, J=8.3 Hz, 2H). Anal. calcd for $C_{26}H_{35}NO_5SSi$ (501.7): C, 62.24; H, 7.03; N, 2.79. Found: C, 62.08; H, 6.91; N, 2.88.

3.1.14. (3*S*,4*S*,5*R*,6*S*)-5-Benzyloxy-6-(*tert*-butyl-dimethyl-silyloxymethyl)-3,4-dihydroxy-1-(toluene-4-sulfonyl)-piperidin-2-one (16). To a stirred solution of alkene **15** (0.81 mg, 1.62 mmol), in a mixture of *t*-BuOH/acetone (1:1 v/v, 20 mL), NMO (0.6 g, 2.75 mmol) and catalytic amount of solution OsO_4 (1 mL) were added. The reaction mixture was run for 6 h, then quenched with Na_2SO_3 (0.42 g, 3 mmol), stirred for 30 min and extracted with EtOAc (2×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to a yellowish slurry which was purified by chromatography (EtOAc/hexane 1:1, R_f 0.3) yielding **16** (0.83 g, 96%) as colorless oil. $[\alpha]_D^{22}$=+67.3 (*c* 0.65, EtOAc); IR (neat): ν_{max} 3420 (OH), 1670 (N–C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.05 (s, 6H), 0.90 (s, 9H), 2.30 (d, J=2.2 Hz, 1H), 2.43 (s, 3H), 2.48 (d, J=2.2 Hz, 1H), 3.40 (m, 1H), 3.82 (dd, J= 10.5, 5.7 Hz, 1H), 3.95 (dt, J=10.5, 5.5 Hz, 1H), 4.01 (dd, J=10.5, 6.1 Hz, 1H), 4.08 (m, 1H), 4.16 (dt, J=10.7, 5.7 Hz, 1H), 4.23 (d, J=11.4 Hz, 1H), 4.65 (d, J=11.4 Hz, 1H), 7.16 (dd, J=5.7, 3.5 Hz, 2H), 7.27 (d, J=8.3 Hz, 2H), 7.30 (m, 3H), 7.83 (d, J=8.3 Hz, 2H). Anal. calcd for $C_{26}H_{37}NO_7SSi$ (535.7): C, 58.29; H, 6.96; N, 2.61. Found: C, 58.37; H, 7.11; N, 2.54.

3.1.15. (1*S*,3*S*,6*S*,7*R*)-7-Benzyloxy-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-5-(toluene-4-sulfonyl)-tetrahydro-[1,3]dioxolo[4,5-*c*]-pyridin-4-one (17). To a stirred solution of piperidin-2-one **16** (0.73 g, 1.36 mmol) and 2,2-dimethoxypropane (0.84 mL, 6.8 mmol) in dry acetone (2 mL), *p*-TsOH (5 mg, 0.02 mmol) was added. The reaction was run for 5 h, then quenched with sat. $NaHCO_3$ (10 mL) and extracted with EtOAc (2×20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to a yellowish slurry which was purified by chromatography (EtOAc/hexane 1:4, R_f 0.55) yielding **17** (0.71 g, 90%) in pure white crystalline form. Mp 118–119°C (Et_2O/hexane); $[\alpha]_D^{22}$=+44.1 (*c* 0.3, EtOAc); IR (neat): ν_{max} 1670 (N–C═O) (C═O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.03 (s, 6H), 0.88 (s, 9H), 1.34 (s, 3H), 1.39 (s, 3H), 2.23 (s, 3H), 3.50 (m, 1H), 3.69 (m, 1H), 3.80–3.92 (m, 2H), 4.01 (m, 2H), 4.36 (d, J=11.8 Hz, 1H), 4.60 (d, J=11.8 Hz, 1H), 7.15 (d, J=7.5 Hz, 2H), 7.23 (d, J=8.3 Hz, 2H), 7.31 (m, 3H), 7.60 (d, J=8.3 Hz, 2H). Anal. calcd for $C_{29}H_{41}NO_7SSi$ (575.8): C, 60.49; H, 7.18; N, 2.43. Found: C, 60.74; H, 7.40; N, 2.29.

3.1.16. (1*S*,3*S*,6*S*,7*R*)-7-Benzyloxy-6-hydroxymethyl-2,2-dimethyl-5-(toluene-4-sulfonyl)-tetrahydro-[1,3]-dioxolo[4,5-*c*]pyridin-4-one (18). To a solution of **17**

(0.66 g, 1.15 mmol) in THF (13 mL), TBAF (1.0 M solution in THF, 1.7 mL) was added. The mixture was stirred for 2 h, and the solvent was evaporated under reduced pressure. The resulting yellowish slurry was purified by chromatography (EtOAc/hexane 3:2, R_f 0.25) to give alcohol **18** (0.48 g, 92%) as a white solid. Mp 155–156°C (decomp.); $[\alpha]_D^{22}$=+76.8 (*c* 0.3, EtOAc); IR (neat): ν_{max} 1665 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.34 (s, 3H), 1.39 (s, 3H), 2.30 (s, 3H), 3.10 (d, *J*=6.2 Hz, 1H), 3.47 (m, 1H), 3.67 (dd, *J*=10.1, 6.2 Hz, 1H), 3.79 (m, 1H), 3.92–4.01 (m, 3H), 4.36 (d, *J*=11.8 Hz, 1H), 4.60 (d, *J*=11.8 Hz, 1H), 7.15 (d, 7.5 Hz, 2H), 7.23 (d, *J*=8.3 Hz, 2H), 7.31 (m, 3H), 7.60 (d, *J*=8.3 Hz, 2H). Anal. calcd for $C_{23}H_{27}NO_7S$ (461.5): C, 59.85; H, 5.90; N, 3.03. Found: C, 59.73; H, 5.66; N, 3.15.

3.1.17. (1*S*,3*S*,6*R*,7*R*)-7-Benzyloxy-2,2-dimethyl-4-oxo-5-(toluene-4-sulfonyl)-hexahydro[1,3]dioxolo[4,5-*c*]pyridin-6-carboxylic acid (19). To a stirred solution of **18** (0.46 g, 1 mmol) in a mixture of $H_2O/CCl_4/CH_3CN$ (1.5:1:1 v/v, 7.5 mL), $NaIO_4$ (0.84 g, 4.0 mmol) and $RuCl_3$ (4.5 mg, 0.018 mmol) catalyst were added. The mixture was stirred for 2 h, quenched with propan-2-ol and filtered through a celite pad. The filtrate was evaporated to a yellowish slurry which was purified by chromatography ($CHCl_3$/MeOH 3:2 R_f 0.4) yielding **19** (0.42 g, 85%) as a foamy solid. $[\alpha]_D^{22}$=+41.1 (*c* 0.3, MeOH); IR (neat): ν_{max} 1735 (C=O), 1670 (N–C=O) cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$): δ_H 1.36 (s, 3H), 1.40 (s, 3H), 2.39 (s, 3H), 3.72 (m, 1H), 3.95–4.08 (m, 2H), 4.36 (d, *J*=12.0 Hz, 1H), 4.45 (d, *J*=12.0 Hz, 1H), 4.98 (m, 1H), 7.18 (d, *J*=7.9 Hz, 2H), 7.25 (d, *J*=8.3 Hz, 2H), 7.39 (m, 3H), 7.68 (d, *J*=8.3 Hz, 2H). Anal. calcd for $C_{24}H_{27}NO_8S$ (489.5): C, 58.88; H, 5.56; N, 2.86. Found: C, 58.67; H, 5.51; N, 2.96.

3.1.18. (2*R*,3*R*,4*S*,5*S*)-3,4,5-Trihydroxy-6-oxo-1-(toluene-4-sulfonyl)-piperidine-2-carboxylic acid (20). A solution of compound **19** (0.4 g, 0.82 mmol) in MeOH (4 mL) was hydrogenated over 10% Pd/C (40 mg) under 1 bar pressure for 4 h. The catalyst was removed by filtration through celite and *p*-TsOH·H_2O (2.3 mg, 0.09 mmol) was added. The reaction was stirred for 1 h, concentrated and purified by chromatography ($CHCl_3$/MeOH 3:2 R_f 0.18) yielding **20** (0.14 g, 80%) as an off-white solid. Mp 255–259°C (decomp.); $[\alpha]_D^{22}$=+73.8 (*c* 0.3, MeOH); IR (neat): ν_{max} 3420–3370 (OH), 1675 (N–C=O), 1730 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO): δ_H 2.40 (s, 3H), 3.50 (dd, *J*=12.1, 1.5 Hz, 1H), 4.38 (dd, *J*=2.8, 4.8 Hz, 1H), 4.21 (m, 1H), 4.35 (d, *J*=3.5 Hz, 1H), 4.60 (s br, 1H), 7.25 (d, *J*=8.3 Hz, 2H), 7.68 (d, *J*=8.3 Hz, 2H). Anal. calcd for $C_{13}H_{15}NO_8S$ (345.3): C, 45.21; H, 4.38; N, 4.06. Found: C, 45.12; H, 4.44; N, 3.80.

3.1.19. (2*R*,3*R*,4*S*,5*S*)-3,4,5-Trihydroxy-6-oxo-piperidine-2-carboxylic acid (21). To a solution of naphthalene (0.3 g, 2.34 mmol) in freshly distilled THF (10 mL), sodium (55 mg, 2.3 mmol) was added. After 45 min of stirring at ambient temperature (dark-green color), the mixture was cooled to −78°C and a solution of compound **20** (130 mg, 0.376 mmol) in THF (3 mL) was added. The reaction mixture was stirred at that temperature for 30 min, quenched with sat. NH_4Cl (15 mL) and extracted with $CHCl_3$ (3×15 mL). The solvent was evaporated to give the target molecule **21** (42 mg, 58%). An analytically pure sample was obtained as white prisms by crystallization from MeOH/Et_2O. Mp 260–265°C (decomp.). $[\alpha]_D^{22}$=+103.5 (*c* 0.3, MeOH); IR (neat): ν_{max} 3420–3370 (OH), 3250 (NH), 1670 (N–C=O), 1725 (C=O) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ_H 4.19 (m, 1H), 4.25 (dd, *J*=2.8, 4.8 Hz, 1H), 4.40 (d, *J*=3.5 Hz, 1H), 4.80 (s br, 1H). Anal. calcd for $C_6H_9NO_6$ (191.1): C, 65.54; H, 6.42; N, 2.55. Found: C, 65.39; H, 6.44; N, 2.71.

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