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Scalable synthesis of (−)-*trans*-3-hydroxypipecolic acid via a useful chiral building block

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A R T I C L E I N F O

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A B S T R A C T

A scalable synthesis of (−)-*trans*-2-(hydroxymethyl)-1,2,3,6-tetrahydropyridin-3-ol, a versatile chiral building block is described along with its transformation to (−)-*trans*-3-hydroxypipecolic acid.

1. Introduction

Tetrahydropyridinol **1**, or its variously protected forms, is a common key building block or intermediate in numerous papers targeting the synthesis of nojirimycin analogs **2** and other iminosugars including sialic acid analogs **3** (Fig. 1).[1,2]

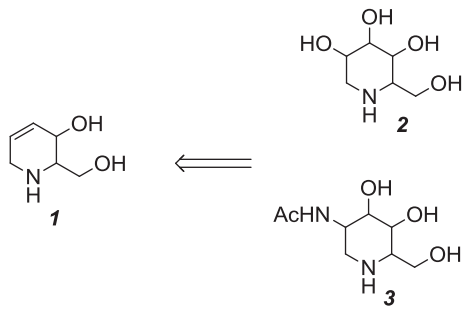

Fig. 1. Uses for the chiral building block **1**.

We required an economical, scalable access to **8** in enantio- and diastereopure form as part of one of our projects. The project was discontinued sometime after successful delivery of over 10 g of the target compound (**8**) in one batch. Due to the continued interest of the synthetic community in derivatives of **1**,[3] we wish to convey the full details for the preparation of **8**. The synthesis is a modified and streamlined version of the synthesis we used to synthesize deoxyaltronojirimycin.[4]

2. Results and discussion

The synthesis is outlined in Scheme 1 and begins with Garner's aldehyde **4**.[5] Garner's aldehyde, while expensive to purchase, is readily prepared at moderate scale.[6] The largest batches prepared were in excess of 130 mmol with >98% ee through DIBAL-H reduction of the corresponding methyl ester. Lithium acetylide (1.3 equiv) generated from silyl protected propargyl alcohol was reacted with **4** to give the propargylic alcohol as a mixture of diastereomers (ca. 15:1 *anti*:*syn* by ^{1}H NMR spectroscopy) in high yield (typically >95%). This reaction was originally described by Jurczak[7] and we found that improved *anti* selectivity is obtained by using THF as the solvent and slowly adding the aldehyde as a *precooled* solution. The crude product was treated with NaH in the presence of BnBr/NaI in a DMF/THF mixture to introduce the benzyl protection. After work up, the reaction mass was filtered through a pad of silica gel to remove any polar impurities/color that might have formed during the previous step. The greasy nature of the compound is highly advantageous as it permits extraction of the product from aqueous DMF mixtures with hydrocarbon solvents, such as hexane and facilitates the silica gel filtration. The silyl protecting group was removed by treatment with ammonium bifluoride in methanol. Ammonium bifluoride is inexpensive and does not generate bothersome tetrabutylammonium impurities associated with TBAF. The crude mass was then loaded on a pad of silica gel and washed with hexane to remove non-polar impurities

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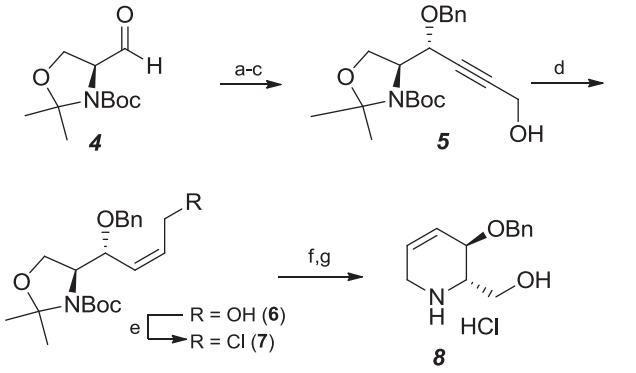
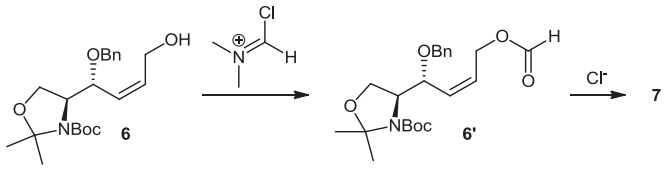
(e.g., excess BnBr) to give **5** in high purity and yield (91% crude yield from **4**) avoiding fractionation by column chromatography.



Scheme 1. Reagents and conditions: a) HC≡CCH$_2$OTBS, *n*-BuLi, THF, −78 °C, then **4**; b) NaH, BnBr, NaI, DMF/THF, 0 °C; c) $NH_4 \cdot HF_2$, MeOH, rt, then silica gel, 91% over 3 steps; d) Lindlar's catalyst, quinoline, H_2, benzene, rt, 98%; e) $POCl_3$, DMF, rt 81%. f) AcCl, MeOH; rt. g) Basic ion exchange resin, MeOH, then cryst from ^{i}PrOH/EtOH, 69% over two steps.

Lindlar reduction was used to introduce the *Z*-double bond into the molecule.[8] Typically 5% of the *E*-double bond was formed as evidenced by ^{1}H NMR spectroscopy, but this is of no consequence as this impurity is completely removed during the final crystallization. High purity **6** was obtained in 98% crude yield after filtering off the catalyst and acidic washings, thus obviating any need for purification.

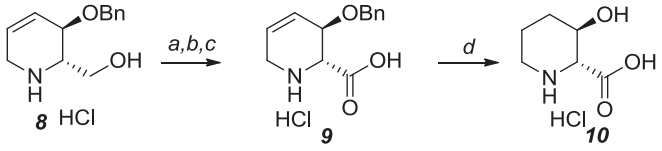
A leaving group had to be introduced to the allylic position. We first considered preparing sulfonate esters (mesylate, tosylate) of the primary alcohol. They both worked admirably in the pivotal cyclization, but both gave the same impurity during their formation. The impurity was readily identified as the allyl chloride **7**. The chloride possessed improved stability and cleaner reaction profile during the cyclization over the sulfonate esters and was targeted for the synthesis. Initial experiments for the chlorination were conducted with PCl_5 and showed promising results on small scale (>90% isolated yield). However, on scale-up, the yields unexplainably dropped to about 50%. Most likely the traces of chlorine in the reagent were the culprit. Fortunately, $POCl_3$ in DMF proved to be an excellent replacement, providing the allyl chloride in high yield. Interestingly, no reaction took place with 1 equiv of $POCl_3$. With 2 equiv fast formation of an intermediate product was first seen with slower conversion to the chloride. The intermediate was isolated and identified as the formate ester **6′**. Thus, the alcohol is initially formylated with the Vilsmeier reagent produced from $POCl_3$ and DMF (Scheme 2). The formate is then displaced by chloride to give the product and formic acid. We encountered a slight problem during the workup on scale; too rapid addition of NaOH caused partial hydrolysis of the product back to the allyl alcohol or a related compound. Fortunately, the impurity could be removed during product isolation. The allyl chloride **7** was obtained in 81% crude yield.



Scheme 2. Chlorination of **6** via a formate ester.

The protecting groups were most efficiently removed using methanolic HCl generated from acetyl chloride. Other acids tested (TFA, TsOH) complicated the product isolation after cyclization, which was accomplished by treating a methanolic solution of the crude acid with basic ion exchange resin at elevated temperature. This enabled the cyclization and after crystallization from ^{i}PrOH/EtOH the product was obtained as a stable, non-hygroscopic hydrochloride salt in 69% isolated yield. The use of ion exchange resin was highly beneficial as traditional bases (TEA, DIPEA) caused the hydrochloride salt to be contaminated with the salt of the base, requiring multiple crystallizations to upgrade the purity. Use of inorganic bases (K_2CO_3, $NaHCO_3$) avoided that problem, but contaminated the crystalline material with inorganics. Otherwise the crystallization is robust, efficiently removing impurities from the upstream chemistry (e.g., the isomeric impurity from the hydrogenation) even at elevated levels.

The utility of **8** was demonstrated by transforming it into *trans*-3-hydroxypipecolic acid **10** (Scheme 3).[9] We initially attempted to oxidize **8** directly to **9** under various conditions with little success. Either the reactions did not proceed or more often were messy with plenty of over oxidized compounds detected. On the other hand, the high solubility of **9** into aqueous phases limited our choice of oxidants to organic ones. Therefore, compound **8** was Boc protected and then subjected to TEMPO catalyzed oxidation with bis(acetoxy) iodobenzene (BAIB) as the terminal oxidant to relatively cleanly give the carboxylic acid.[10] We found it useful to perform the reaction under biphasic conditions in the presence of sodium bicarbonate. This way the workup was facilitated and the product was partly protected from over oxidation as the sodium carboxylate had very limited solubility in the reaction mixture. After extractive workup the transient Boc-group was cleaved by exposure to HCl in acetonitrile. The crude **9** was efficiently purified by slurrying it in ^{i}PrOH–heptane mixture to give pure **9** as a white powder in 63% yield over three steps. Final hydrogenation delivered **10** as a colorless crystalline solid entirely without chromatography.



Scheme 3. Reagents and conditions: a) Boc_2O, NEt_3, CH_2Cl_2, rt; b) cat. TEMPO, BAIB, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C to rt; c) HCl, MeCN, rt to 50 °C, 63% over three steps; d) Pd/C, H_2, EtOH, rt, 97%.

3. Conclusion

In conclusion, we have developed a scalable route to tetrahydropyridinol **8** in seven steps from Garner's aldehyde and in 50% overall yield. The absence of chromatography enables rapid processing (<1.5 weeks by a single person) and the robust crystallization ensures high product quality. These factors, coupled with low-cost reagents, make this route highly desirable for lab-scale synthesis of this intermediate. Furthermore, the intermediate **8** was quickly transformed into *trans*-3-hydroxypipecolic acid in 60% yield also entirely without chromatography.

4. Experimental section

4.1. General

Dry dichloromethane and tetrahydrofuran were obtained from a solvent drier (MB SPS-800, neutral alumina). Dimethyl formamide was from a freshly opened bottle. Other solvents used in reactions and in chromatography were of p.a. quality. Reagents were obtained from

Sigma–Aldrich or from Acros Organics and used as such, unless otherwise stated. TLC monitoring was performed on Merck silica gel 60 F_{254} (230–400 mesh, aluminum) plates. UV-light (λ=254 nm), and permanganate (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 1 M NaOH, diluted to 300 mL with water) or vanillin (3 g vanillin, 2.5 mL concd H_2SO_4, 1.5 mL acetic acid, 125 mL EtOH) stains were used to visualize the plates. Flash chromatography was performed on Merck Silica Gel 60 silica. The Celite used in filtrations was either Fluka Celite 501 or Sigma–Aldrich Celite 535 Coarse. NMR spectra were recorded on Bruker Avance 400 spectrometer. The spectra were calibrated either to TMS (^{1}H: δ 0.00 ppm), MeOD (^{1}H: TMS, ^{13}C δ: 49.86 ppm), $CDCl_3$ (^{13}C: δ 77.0 ppm), $Cl_2CDCDCl_2$ (^{1}H: δ 6.00 ppm, ^{13}C δ: 73.8), toluene-d_8 (^{1}H: δ 2.09 ppm, ^{13}C δ: 20.4) or to D_2O (^{1}H: δ 4.70 ppm, ^{13}C: δ 49.5 ppm, MeOH as internal standard) depending on the used solvent. Spectra were recorded at 25 °C, unless otherwise stated. Heating of the NMR-samples was performed using a probe heater. IR spectra were recorded on Perkin–Elmer Spectrum One FTIR machine. Optical rotations were measured with Perkin–Elmer 343 polarimeter using sodium lamp and a 10 cm quartz cuvette. Melting points were measured with Stuart SMP30 melting point apparatus. HRMS spectra were recorded on Waters Micromass LCT Premier (ESI/TOF) mass spectrometer.

4.2. (*S*)-*tert*-Butyl 4-((*R*)-1-(benzyloxy)-4-hydroxybut-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (5)

A flame-dried flask under argon was charged with O-TBS propargyl alcohol (23.7 g, 138 mmol, 130 mol-%) and 275 mL of dry THF. The solution was cooled to −78 °C and *n*-BuLi (57.5 mL, 135 mmol, 125 mol %, 2.35 M in hexanes) was added over 10 min. The resulting mixture was stirred for an hour. Then 4 (22.7 g, 98.8 mmol, 100 mol %) was added as a THF solution (115 mL+20 mL for washing, precooled to −78 °C) via cannula over 1 h. The resulting solution was stirred for 1 h and then quenched by adding 100 mL of satd NH_4Cl. The cooling bath was removed and replaced with a warm water bath. After reaching room temperature, the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to yield 42.3 g of crude product as slightly yellow oil. An analytical sample was prepared by flash chromatography (10% EtOAc/hexanes) to afford a colorless oil. R_f 0.56 (2:1 Hex/EtOAc); $[\alpha]_D^{20}$ −39.6 (*c* 2.50, CH_2Cl_2) lit.[7] −40.7 (c 1.1 $CDCl_3$); ^{1}H NMR (400 MHz, C_6D_6, 60 °C): δ 4.64 (br s, 1H), 4.21 (d, *J*=2.0, 2H), 4.00 (m, 2H), 3.72 (dd, *J*=8.5, 7.2, 1H), 1.69 (s, 3H), 1.46 (s, 3H), 1.39 (s, 9H), 0.94 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 154.1, 94.9, 84.5, 52.5, 81.3, 65.0, 64.1, 62.5, 51.6, 28.3, 25.7, 25.8 (rotamers), 25.2, 18.2, −5.2; HRMS: calcd for $C_{20}H_{37}NO_5Si$+Na 422.2339, found 422.2337.

A flask under argon was charged with the crude product from the previous reaction (42.3 g, assumed circa 98.0 mmol, 100 mol %), and dry DMF (100 mL). The solution was cooled to 0 °C and benzyl bromide (15.4 mL, 130 mmol, 130 mol %) was added together with KI (830 mg, 5 mmol, 5 mol %). Finally sodium hydride (4.8 g, 120 mmol, 120 mol %, 60% dispersion in mineral oil) was added in a single portion. After gas evolution had stopped the slurry was diluted with 100 mL of dry THF. After 1 h of stirring, the reaction was quenched by adding 60 mL of satd $NaHCO_3$ (dropwise at first, until gas no longer forms) and then diluted with 150 mL of water. The mixture was extracted with EtOAc (3×100 mL). The combined organic phases were washed with water (200 mL) and brine, dried over Na_2SO_4 and concentrated. The residue was filtered through a pad of silica gel (eluted with 5% EtOAc/Hexanes) to yield 52.4 g of light yellow oil. An analytical sample was prepared by flash chromatography (5% EtOAc/hexanes) to afford a colorless oil. R_f 0.66 (30% EtOAc/Hex); $[\alpha]_D^{20}$ −76.5 (*c* 2.0, CH_2Cl_2); IR (film): 1705, 1390, 1366, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.39 (m, 5H), 4.83 (app. t, *J*=11.3 Hz, 1H), 4.69–4.74 (m, 0.5H, rotamers), 4.51 (dd, *J*=12.1, 7.2 Hz, 1H), 4.45–4.48 (m, 0.5H, rotamers), 4.37 (d, *J*=13.4 Hz, 2H), 4.23–4.29 (m, 1H), 4.09–4.15 (m, 0.5H rotamers), 4.01 (app t, *J*=8.2 Hz, 1H), 3.95–3.99 (m, 0.5H, rotamers), 1.66–1.28 (m, 15H), 0.91 (app d, *J*=4.8 Hz, 9H), 0.13 (app d, *J*=5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 152.0, 138.3, 137.9, 128.9, 128.7, 128.5, 128.3, 128.0, 95.4, 94.8, 81.8, 80.7, 80.3, 71.4, 71.2, 68.3, 67.7, 65.1, 64.7, 61.1, 60.8, 52.2, 28.8, 26.6, 26.3, 26.2, 26.0, 25.6, 24.1, 18.7, −4.6 (ca. 2:1 mixture of rotamers); ^{13}C NMR ($Cl_2DCCDCl_2$, 90 °C): δ 137.9, 128.2, 128.1, 127.7, 127.4, 94.5, 86.2, 81.5, 79.8, 71.0, 64.2, 60.6, 53.3, 51.5, 28.3, 25.9, 25.7, 25.5, 18.0, −5.2 (the carbonyl group resonance is lost at this temperature); HRMS: calcd for $C_{27}H_{43}NO_5Si$+Na 512.2832, found 512.282.

The product from the previous reaction (52.8 g, assumed circa 98 mmol, 100 mol %) was dissolved in MeOH (80 mL) under ambient conditions. $NH_4 \cdot HF_2$ (11.5 g, 200 mmol, 200 mol %) was added and the resulting mixture was stirred for 18 h. To quench the reaction, 30 g of silica gel was added to the reaction mixture. After 30 min of stirring, the solution was diluted with 350 mL of CH_2Cl_2, passed through a pad of silica (washed with 10% MeOH/CH_2Cl_2) and concentrated. The crude product was dissolved in 20% EtOAc/hexanes and loaded onto a pad of silica gel, which was washed with hexanes followed by EtOAc. After concentration a yellow oil was obtained (34.0 g, 91% over three steps). An analytical sample was prepared by flash chromatography (25% EtOAc/hexanes) to afford a colorless oil. R_f 0.47 (1:1 EtoAc/Hex); $[\alpha]_D^{20}$ −54.9 (*c* 1.0, CH_2Cl_2); IR (film): 3436, 2978, 1683, 1392, 1366 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 7.21–7.40 (m, 5H), 4.80 (d, *J*=12.1 Hz 1H), 4.52 (d, *J*=12.1 Hz, 1H), 4.12–4.36 (m, 4H), 3.93–4.06 (m, 1H), 1.27–1.70 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 151.5, 137.6, 137.3, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 94.9, 94.2, 85.7, 85.4, 82.5, 80.4, 79.9, 70.9, 67.9, 97.8, 64.6, 64.4, 60.4, 60.1, 50.7, 28.3, 26.5, 25.5, 24.8, 23.5 (rotamers); HRMS: calcd for $C_{21}H_{29}NO_5$+Na 398.1943, found 398.1953.

4.3. (*S*)-*tert*-Butyl 4-((*R*,*Z*)-1-(benzyloxy)-4-hydroxybut-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (6)

A 500 mL flask was charged with benzene (50 mL), Pd/$CaCO_3$/Pb (2.54 g, 1.2 mmol, 1.5 mol %, 5% in Pd) and quinoline (3.3 mL, 27.8 mmol, 35 mol %). The mixture was degassed three times and left to stir under argon for 30 min. Then **5** (29.8 g, 79.5 mmol, 100 mol %) was added in a benzene solution (200 mL) and H_2 atmosphere was introduced. The mixture was stirred vigorously for 2.75 h (rxn complete by NMR), filtered through a pad of Celite and concentrated. The residue was dissolved in EtOAc (150 mL) and washed with 1 M HCl (100 mL) to remove quinoline. The organic layer was dried over Na_2SO_4 and concentrated to give the crude product (29.4 g, 98%) as a slightly yellow oil. An analytical sample was prepared by flash chromatography (20% EtOAc/hexanes) to afford a colorless oil. R_f 0.43 (80% Et_2O/Hex); $[\alpha]_D^{20}$ −65.0 (*c* 1.00, Et_2O); IR: 3436, 1698, 1391, 1366 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.30–7.12 (m, 5H), 5.79 (dddd, *J*=0.9, 6.1, 7.3, 11.3 Hz, 1H), 5.43 (t, *J*=9.2 Hz, 1H), 4.52 (d, *J*=11.7 Hz, 1H), 4.43 (br s, 0.5H), 4.27 (d, *J*=11.7 Hz, 1H), 4.21–3.96 (m, 4H), 3.91–3.72 (m, 2H), 2.82 (br s, 0.5H), 1.57–1.23 (m, 15H); ^{1}H NMR (400 MHz, $Cl_2CDCDCl_2$, 80 °C): δ 7.40–7.28 (m, 5H), 5.89 (dddd, *J*=1.1, 6.2, 7.0, 11.3 Hz, 1H), 5.56 (tdd, *J*=1.3, 9.5, 11.0 Hz, 1H), 4.63 (d, *J*=12.1 Hz, 1H), 4.52 (br s, 1H), 4.45 (d, *J*=11.7 Hz, 1H), 4.28–4.12 (m, 3H), 4.01–3.91 (m, 2H), 1.60 (s, 3H), 1.53 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $Cl_2CDCDCl_2$, 80 °C): δ 152.3, 138.3, 133.2, 130.6, 128.1, 127.6, 127.4, 94.1, 80.0, 74.1, 70.8, 64.2, 60.5, 58.5, 28.3, 26.6; HRMS: calcd for $C_{21}H_{31}NO_5$+Na 400.2100, found 400.2115.

4.4. (*S*)-*tert*-Butyl 4-((*R*,*Z*)-1-(benzyloxy)-4-chlorobut-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (7)

To an ice cooled, stirred solution of **6** (29.4 g, 77 mmol, 100 mol %) in DMF (210 mL) was added $POCl_3$ (15.6 mL, 170 mmol, 220 mol %) under argon. The cooling bath was removed and the solution was stirred overnight. The bright orange reaction was

quenched by cooling to 0 °C and slowly adding 2 M NaOH (ca. 250 mL) to a pH of >7. The mixture was extracted with EtOAc (3×180 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. During the neutralization another product had formed, with R_f value similar to the starting material. Filtration through a pad silica (eluted with 15% EtOAc/hexanes) yielded the product (24.7 g, 81%) as a colorless oil. No trace of the byproduct could be found. An analytical sample was prepared by flash chromatography (20% EtOAc/hexanes) to afford a colorless oil. R_f 0.59 (60% Et_2O/Hex); $[\alpha]_D^{20}$ −61.5 (*c* 1.00, CH_2Cl_2); IR (film) 1699, 1384, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.16 (m, 5H), 5.88–5.73 (m, 1H), 5.54 (q, *J*=11.2 Hz, 1H), 4.54 (dd, *J*=8.1, 11.7 Hz, 1H), 4.40–4.32 (m, 0.5H), 4.29 (d, *J*=11.7 Hz, 1H), 4.26–4.19 (m, 0.5H), 4.13–3.73 (m, 5H), 1.57–1.28 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 151.9, 137.9, 137.6, 132.5, 130.2, 129.8, 128.5, 128.3, 128.0, 127.9, 127.6, 94.5, 93.8, 80.1, 73.3, 70.8, 64.8, 64.2, 60.4, 59.8, 39.9, 38.9, 28.4, 28.3, 27.1, 26.6, 24.6, 23.0 (rotamers); ^1H NMR (400 MHz, $Cl_2CDCDCl_2$, 90 °C): δ 7.41–7.29 (m, 5H), 5.94–5.86 (m, 1H), 5.65 (dd, *J*=9.5, 10.6 Hz, 1H), 4.65 (d, *J*=11.7 Hz, 1H), 4.54–4.48 (m, 1H), 4.45 (d, *J*=12.1 Hz, 1H), 4.21 (dd, *J*=8.4, 11.3 Hz, 1H), 4.16 (d, *J*=6.6 Hz, 1H), 4.11 (dd, *J*=7.3, 12.1 Hz, 1H), 3.96 (td, *J*=6.2, 6.3 Hz, 1H), 4.01–3.93 (m, 1H), 1.61 (s, 3H), 1.55 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $Cl_2CDCDCl_2$, 90 °C): δ 138.1, 132.5, 129.6, 128.2, 127.7, 127.5, 94.1, 79.9, 73.9, 71.0, 64.3, 60.3, 39.2, 28.3, 26.7; HRMS calcd for $C_{21}H_{30}NO_4Cl$+Na 418.1761, found 418.1736.

4.5. ((2*S*,3*R*)-3-(Benzyloxy)-1,2,3,6-tetrahydropyridin-2-yl) methanol hydrochloride (8)

Acetyl chloride (30 mL, 420 mmol) was added to ice cooled methanol (90 mL) under argon over 10 min. The solution was stirred for 30 min and then poured over neat **7** (24.7 g, 62.0 mmol, 100 mol-%). After 30 min of stirring at room temperature, the starting material was completely consumed according to TLC. The solvent was evaporated in vacuo to yield 18.9 g of crude product as a blood red/brown glassy substance.

The crude product was dissolved in methanol. Then ion exchange resin (Merck ionenaustauscher II; weakly basic tertiary amine resin, 20 g, 5 meq/g, moist, ca. 200 mol %) was added and the mixture was vigorously stirred until the solution became neutral. Then the mixture was filtered through a sintered glass funnel and concentrated. The residue was dissolved in 15 mL *i*-PrOH and 15 mL EtOH and stirred for 16 h at 75 °C. Upon cooling 3.4 g of fine microcrystalline powder was obtained. The mother liquor was concentrated and dissolved in methanol. Another 20 g batch of the resin was added to neutralize the pH. The mixture was heated to reflux and after 2 h filtered through a sintered glass funnel and concentrated. The now solid crude was crystallized from *i*-PrOH/EtOH to yield 6.7 g of medium sized needles. A second crop yielded 840 mg of the said needles for a total of 10.94 g (69%, 50% over seven steps). R_f 0.66 (10% MeOH/CH_2Cl_2+1% 25% aqueous ammonia); mp: 196 °C; $[\alpha]_D^{20}$ −109.1 (*c* 1.00, MeOH); IR (KBr disc) 3320, 1585, 1087 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.40–7.26 (m, 5H), 6.14 (dddd, *J*=1.1, 7.4, 8.7, 11.0 Hz, 1H), 5.96–5.89 (m, 1H), 4.71 (d, *J*=11.5 Hz, 1H), 4.63 (d, *J*=11.5 Hz, 1H), 4.24–4.18 (m, 1H), 3.87 (dd, *J*=11.9, 3.8 Hz, 1H), 3.79–3.70 (m, 2H), 4.23 (ddt, *J*=17.4, 3.5, 1.8 Hz, 1H), 3.42 (dt, *J*=6.7, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 139.9, 130.3, 130.0, 129.9, 128.4, 124.5, 73.3, 70.4, 59.4, 59.3, 42.8; HRMS: calcd for $C_{13}H_{17}NO_2$+H 220.1338, found 220.1340; Anal. Calcd for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.48; found: C, 61.22; H, 6.84; N, 5.46.

4.6. (2*R*,3*R*)-3-(Benzyloxy)-1,2,3,6-tetrahydropyridine-2-carboxylic acid hydrochloride (9)

To a stirred mixture of **8** (2.00 g, 8.85 mmol, 100 mol %) in CH_2Cl_2 (20 mL) was added triethylamine (2.78 mL, 19.9 mmol, 225 mol %) followed by Boc_2O (2.42 g, 11.1 mmol, 125 mol %). The mixture was stirred for 2 h and then poured into 1 N HCl (20 mL). The organic phase was washed with 1 N HCl (20 mL) and the combined aqueous phases were back extracted with CH_2Cl_2 (1×20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give 3.42 g of crude as a light yellow oil.

The crude (assumed 8.85 mmol, 100 mol %) was dissolved in CH_2Cl_2 (30 mL). $NaHCO_3$ (1.50 g, 17.7 mmol, 200 mol %) was added as a solution in water (30 mL). The resulting vigorously stirred biphasic mixture was cooled to 0 °C and TEMPO (275 mg, 1.77 mmol, 20 mol %) was added followed by BAIB (6.27 g, 19.5 mmol, 220 mol %). After circa 20 min of reaction a thick slurry had formed, which is most likely the sodium salt of the product. The mixture was stirred for 16 h and then quenched with 10% aqueous $Na_2S_2O_3$ (8 mL). 2 N KOH (20 mL) was added and the phases were separated. The organic phase was diluted with MTBE (30 mL) and extracted with 2 N KOH (1×20 mL). The combined aqueous phases were washed with MTBE (1×30 mL) and carefully acidified with 3 N HCl at 0 °C. The turbid mixture was extracted with MTBE (3×35 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated to give 2.17 g of the crude acid as slightly yellow oil.

The crude product (2.17 g, assumed 6.5 mmol, 100 mol %) was dissolved in MeCN (15 mL) and then HCl (2.3 mL, 22.8 mmol, 32% aq) was added at 0 °C. The solution was allowed to warm to rt and then gently heated to 50 °C for 2 h to finish the deprotection. The mixture was concentrated to a cream colored solid. The solid was slurried in a mixture of *i*-PrOH and heptane (1:2, 10 mL) at 50 °C for 2 h, then cooled to rt and placed in an ice bath to finalize the precipitation. The product was isolated by filtration and the filter cake was washed with 50% EtOAc/heptane to give **9** (1.52 g, 63% over three steps) as a white powder. Mp 187–189 °C (decomp.); $[\alpha]_D^{20}$ −105.8 (*c* 1.00, MeOH); IR (KBr disc) 2965, 1743, 1567, 1440, 1420, 1211 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.51–7.40 (m, 5H), 6.11 (ddt, *J*=10.5, 4.5, 2.2 Hz, 1H), 6.01 (dt, *J*=10.6, 2.9 Hz, 1H), 4.77 (d, *J*=11.3 Hz, 1H), 4.73 (d, *J*=11.3 Hz, 1H), 4.58 (t, *J*=4.0 Hz, 1H), 4.40 (d, *J*=4.0 Hz, 1H), 3.97 (ddd, *J*=17.7, 4.3, 2.1 Hz, 1H), 3.81–3.72 (m, 1H); ^1H NMR (400 MHz, CD_3OD): δ 7.45–7.28 (m, 5H), 6.11 (ddt, *J*=10.6, 4.6, 2.3 Hz, 1H), 5.99 (dt, *J*=10.6, 3.1 Hz, 1H), 4.74 (d, *J*=11.7 Hz, 1H), 4.69 (d, *J*=11.7 Hz, 1H), 4.55 (d, *J*=3.5 Hz, 1H), 4.46 (t, *J*=4.1 Hz, 1H), 3.96 (ddd, *J*=17.7, 4.0, 2.4 Hz, 1H), 3.72 (dddd, *J*=17.7, 3.3, 2.4, 1.1, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 168.5, 138.8, 129.5, 129.3, 129.1, 125.5, 125.3, 72.5, 69.4, 57.3, 41.2; HRMS calcd for $C_{13}H_{15}NO_3$+H 234.1330, found 234.1131.

4.7. (2*R*,3*R*)-3-Hydroxypiperidine-2-carboxylic acid (10)

To a solution of **9** (1.0 g, 3.7 mmol, 100 mol %) in MeOH (15 mL) was added Pd/C (200 mg, 0.19 mmol, 5 mol %, 10 w % Pd) after which the solution was vacuum degassed followed by introduction of H_2 atmosphere. The mixture was stirred under H_2 for 16 h and then filtered through a pad of Celite and concentrated to give 652 mg (97%) of yellowish partly crystalline solid. The purity was upgraded by suspending the solids in EtOH/$CHCl_3$ (1:3, 5 mL) at 75 °C for 1 h. Then the mixture was cooled to room temperature and filtered. The filter cake was washed with cold EtOH/$CHCl_3$ (1:3) and dried to give **10** (635 mg, 95%) as a white microcrystalline powder with a hint of rosy color. Mp: 178–181 °C (decomp.); $[\alpha]_D^{20}$ −14.6 (*c* 1.10, H_2O), lit. for the enantiomer: +14.2 (*c* 0.95, H_2O),[9f] +14.5 (*c* 0.4, H_2O);[9e] IR (KBr disc) 3173, 2981, 1744, 1404, 1280, 1081 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 4.17 (ddd, *J*=6.4, 6.4, 3.1 Hz, 1H), 3.91 (d, *J*=6.4 Hz, 1H), 3.37–3.32 (m, 1H), 3.16–3.06 (m, 1H), 3.15–3.06 (m, 1H), 2.15–2.03 (m, 1H), 1.92–1.81 (m, 1H), 1.80–1.65 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 67.0, 62.9, 44.2, 30.4, 20.1; (The carbonyl carbon was not visible when run in MeOD); ^1H NMR (400 MHz, D_2O): δ 4.07 (dt, *J*=8.1, 2.9 Hz, 1H), 3.75 (d, *J*=7.9 Hz, 1H), 3.31 (ddd, *J*=12.8, 6.6, 3.8 Hz, 1H), 4.40 (ddd,

J=12.7, 9.2, 3.1 Hz, 1H), 2.01–1.90 (m, 2H), 1.74–1.56 (m, 2H); ^{13}C NMR (100 MHz, D_2O): δ 170.5, 66.0, 61.4, 43.0, 29.2, 19.1; HRMS calcd for $C_6H_{12}NO_3$+H 146.0817, found 146.0815.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.020.

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