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*Published in:*  
TETRAHEDRON

*DOI:*  
10.1016/j.tet.2014.02.020

Published: 01/01/2014

*Document Version*  
Peer reviewed version

*Please cite the original version:*  
Scalable synthesis of \((-\)-trans-3-hydroxypipeolic acid via a useful chiral building block

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ARTICLE INFO

Keywords:
Amino alcohol
Diastereoselective synthesis
Hydroxypipeolic acid

ABSTRACT

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-hydroxypipeolic acid.

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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 imino-sugars including sialic acid analogs \(3\) (Fig. 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 \(1\), 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.

2. Results and discussion

The synthesis is outlined in Scheme 1 and begins with Garner's aldehyde \(4\). Garner's aldehyde, while expensive to purchase, is readily prepared at moderate scale. 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 \(\text{anti:sync}\)) by \(^1\)H NMR spectroscopy) in high yield (typically >95%). This reaction was originally described by Jurczak and we found that improved \(\text{anti}\) selectivity is obtained by using THF as the solvent and slowly adding the aldehyde as a pre-cooled 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.

http://dx.doi.org/10.1016/j.tet.2014.02.020
(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\textsubscript{2}N=CHTBS, n-BuLi, THF, \(-78^\circ\text{C}\), then 4; b) NaH, BnBr, NaI, DMF/THF, 0 °C; c) \(\text{NH}_2\), HF\(_2\), MeOH; d) rt. g) Basic ion exchange resin, MeOH, then cryst from two steps.

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 \(\text{HPrOH}/\text{EtOH}\) the product was obtained as a stable, non-hygrosopic 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\(_2\)CO\(_3\), 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). 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.

Lindlar reduction was used to introduce the Z-double bond into the molecule. Typically 5% of the E-double bond was formed as evidenced by \(^1\text{H}\) 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 POCI\(_3\) 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, POCI\(_3\) in DMF proved to be an excellent replacement, and was targeted for the synthesis. Furthermore, the intermediate 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.

In conclusion, we have developed a scalable route to tetrahydroprydinol 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. Conclusion

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...
for washing, precooled to −20°C. propargyl alcohol (23.7 g, 138 mmol, 130 mol-%) and 275 mL of dry 98.8 mmol, 100 mol %) was added as a THF solution (115 mL). The resulting mixture was stirred for an hour. Then 4 (22.7 g, 120 mol %, 60% dispersion in mineral oil) was added in a single portion. dry DMF (100 mL). The solution was cooled to 0°C and a 10 cm quartz cuvette. Melting points were measured with a warm water bath. After reaching room temperature, the organic phases were dried over Na2SO4 and concentrated to yield 30 g of silica gel was added to the reaction mixture. After 30 min of stirring, the solution was diluted with 350 mL of CH2Cl2, passed through a pad of silica (washed with 10% MeOH/CH2Cl2) and concentrated. The crude product was dissolved in 40% 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. After concentration a white solid was obtained. The product from the previous reaction (52.8 g, assumed circa 98 mmol, 100 mol %) was dissolved in MeOH (80 mL) under ambient conditions. NH4F·H2O (11.5 g, 200 mmol 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 filtered and the filtrate was concentrated. The residue was purified by flash chromatography (10% EtOAc/hexanes) to afford a colorless oil. The resulting mixture was stirred for 1 h and then quenched by adding 100 mL of satd NH4Cl. 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 Na2SO4 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. Rf 0.56 (2:1 Hex/EtOAc); δ 4.12 (m, 0.5H, rotamers), 4.37 (d, J=13.4 Hz, 2H), 4.23–4.29 (m, 1H). 

4.2. (S)-tert-Butyl 4-((R)-1-(benzoxyl)-4-hydroxybut-2-enyl)-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 g, 135 mmol, 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) 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 NH4Cl. 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 Na2SO4 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. Rf 0.56 (2:1 Hex/EtOAc); δ 4.12 (m, 0.5H, rotamers), 4.37 (d, J=13.4 Hz, 2H), 4.23–4.29 (m, 1H).
challenged 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 Na2SO4 and concentrated. During the neutralization another product had formed, with Rf 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. Rf 0.59 (60% Et2O/Hex); [α]D25 61.5 (c 1.00, CH2Cl2); IR (film) 1699, 1384, 1365 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 7.31–7.16 (m, 5H), 5.88–7.53 (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); 13C NMR (100 MHz, CDCl3): δ 152.6, 151.9, 137.9, 137.6, 132.5, 130.2, 129.8, 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, CD2Cl2CDCl3, 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, 3H); 13C NMR (100 MHz, CD2Cl2CDCl3, 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 calc'd for C21H30NO4Cl + Na 418.1761, found 418.1736.

4.5. (2S,3R)-3-(Benzyloxy)-1,2,3,6-tetrahydropyridin-2-yl methyl 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, 0.5 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 solid was crude material 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). Rf 0.66 (10% MeOH/CH2Cl2 + 1% aqueous ammonia); mp: 196 °C; [α]D20 –105.8 (c 1.00, MeOH); IR (KBr disc) 2965, 1743, 1567, 1440, 1210 cm⁻¹; 1H NMR (400 MHz, D2O): 0.75–7.40 (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); 13C NMR (400 MHz, CD3OD): δ 7.45–7.28 (m, 5H), 6.11 (ddt, J = 10.6, 4.6, 2.3 Hz, 1H), 5.99 (dd, 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 (dd, 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 (ddd, J = 17.7, 3.3, 2.4, 1.1 Hz); 1H NMR (100 MHz, CD3OD): δ 168.5, 138.8, 129.3, 129.1, 129.5, 125.3, 72.6, 69.4, 57.3, 41.2; HRMS calc'd for C16H25NO4+ 234.1330, found 234.1131.

4.7. (2R,3R)-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 H2 atmosphere. The mixture was stirred under H2 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/CHCl3 (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/CHCl3 (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.; [α]D20 –14.6 (c 1.10, H2O), lit. for the enantiomer: +14.2 (c 0.95, H2O); +14.5 (c 0.4, H2O); IR (KBr disc) 3173, 2981, 1744, 1404, 1280, 1081 cm⁻¹; 1H NMR (400 MHz, CD3OD): δ 4.17 (ddd, J = 6.4, 6.4, 3.1 Hz, 1H), 3.91 (d, J = 4.5 Hz, 1H), 3.37–3.52 (m, 1H), 3.16–3.06 (m, 1H), 1.31–3.06 (m, 1H), 1.25–2.03 (m, 1H), 1.92–1.81 (m, 1H), 1.80–1.65 (m, 2H); 1H NMR (400 MHz, CD3OD): δ 6.70, 62.9, 44.2, 30.4, 201; (The carbonyl carbon was not visible when run in MeOD); 1H NMR (400 MHz, D2O): δ 4.40 (d, 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,
Acknowledgements

Funding from the National Graduate School of Organic Chemistry and Chemical Biology (to O.K.K.) is gratefully acknowledged.

Supplementary data

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

References and notes