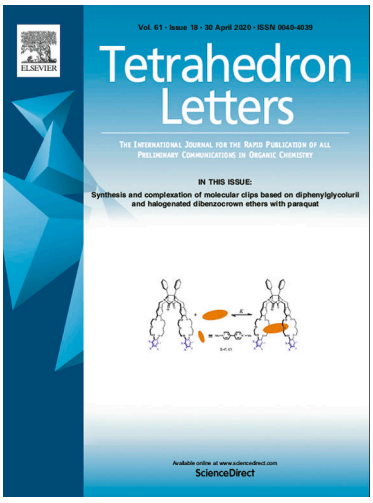
Journal Pre-proofs



A carbohydrate based straightforward approach to *trans*-4-hydroxy-D-proline and *trans*-4-hydroxy-D-prolinol

Umesh Kumar Mishra, Namakkal G. Ramesh

PII: S0040-4039(20)30532-3
DOI: https://doi.org/10.1016/j.tetlet.2020.152081
Reference: TETL 152081

To appear in: *Tetrahedron Letters*

Received Date: 22 April 2020
Revised Date: 21 May 2020
Accepted Date: 23 May 2020

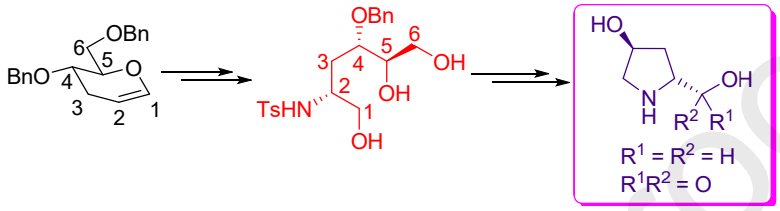
Please cite this article as: Kumar Mishra, U., Ramesh, N.G., A carbohydrate based straightforward approach to *trans*-4-hydroxy-D-proline and *trans*-4-hydroxy-D-prolinol, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152081

Graphical Abstract

A carbohydrate based straightforward approach to *trans*-4-hydroxy-D-proline and *trans*-4-hydroxy-D-prolinol

Umesh Kumar Mishra and Namakkal G Ramesh

Leave this area blank for abstract info.



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

A carbohydrate based straightforward approach to *trans*-4-hydroxy-D-proline and *trans*-4-hydroxy-D-prolinol

Umesh Kumar Mishra and Namakkal G. Ramesh[a,] *

[a] *Department of Chemistry, Indian Institute of Technology Delhi, Hauz Khas, New Delhi – 110016, India.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Trans-4-hydroxy-D-proline
4,6-Di-*O*-benzyl-3-deoxy-D-glucal
Oxidative cleavage
Carbohydrates
Unnatural amino acid

ABSTRACT

Synthesis of *trans*-4-hydroxy-D-proline and the corresponding prolinol has been accomplished starting from 4,6-di-*O*-benzyl-3-deoxy-D-glucal, an enol-ether derived from D-glucose, through oxidative cleavage of a vicinal diol intermediate as the key step. This work represents a practical approach to this unnatural, yet synthetically and biologically very significant, amino acid.

* Corresponding author. Tel.: +91-11-26596584; fax: +91-11-26581102; e-mail: ramesh@chemistry.iitd.ac.in

Introduction

Trans-4-hydroxy-L-proline **1** (Hyp) (Figure 1) is a non-proteinogenic amino acid produced by hydroxylation of proline by the enzyme prolyl 4-hydroxylase during the post translational modification following protein synthesis.[1] Hyp is a major component of the protein collagen and plays a key role in the stabilization of triple helical supercoil of collagen.[2] Hyp rich glycoproteins are vital structural ingredients in the plant cell wall. They participate in the formation of crosslinked networks in the cell wall which is significant for wall strengthening as well as disease resistance.[2] Hydroxyproline is a rich source of reduced carbon and nitrogen.[2] *Trans*-4-hydroxy-D-proline (D-Hyp) **2**, enantiomer of natural Hyp **1**, has also found enormous chemical and biological applications. In 2007, Waffenschmidt reported the isolation of linear hydroxyproline bound *O*-glycans of unicellular green alga *Chlamydomonas reinhardtii* from the outer cell wall of glycoproteins.[3] Through structural identification[3] as well as chemical synthesis,[4] it was established that some of these hydroxyproline bound *O*-glycans such as **3** and **4** are constituted of D-Hyp. It has also been shown that D-Hyp is a promising candidate for the tuning of pharmaceutical, biological or physiochemical properties of *de novo* designed or naturally occurring peptides. Nishizawa et al have shown that an analogue of peptide PYY possessing a combination of *N*-terminal 4-imidazolecarbonyl moiety and three amino acid substitutions D-Hyp, isovalin and c-methylleucine, not only improved the binding affinity of the peptide for Y2R but also increased its anorectic activity in lean mice.[5] D-Hyp based amide **5** has been

developed by Pippel et al as histamine H_3 receptor antagonist.[6] Quinoline bearing proline derivatives such as **6** derived from D-Hyp displayed significant α-amylase inhibitory activity.[7] A series of carboxamides derived from D-Hyp have been tested for their antimicrobial and antifungal activities amongst which compound **7** was found to be the most potent.[8] Conformationally constrained diethylenetriaminepentaacetic acid (DTPA) analogues derived from both Hyp and D-Hyp have been investigated for their complexation with paramagnetic metals such as gadolinium and lutetium.[9] Stereoselective synthesis of *N*-protected alkoxy prolines, including examples from D-Hyp, as potential serine protease factor X_a inhibitors has been reported by Vrieze.[10] Synthesis of novel peptide nucleic acids through the replacement of the hydroxyl group of Boc-protected Hyp and D-Hyp by nucleobases was reported by Lowe.[11] Several *N*-acyl carboxamide derivatives were synthesized from various hydroxyprolines, including D-Hyp, and investigated for their efficacies as inhibitors of human plasma kallikrein.[12] Compound **8**, an inhibitor of cathepsin C, a dipeptidase I, was synthesized from D-Hyp.[13] Hyp and D-Hyp have also found applications as asymmetric catalysts in organic synthesis.[14] As D-Hyp is not naturally occurring, it has to be synthesized and is about 75 times more expensive than natural Hyp. The method originally developed by Robinson,[15] involving epimerization of both the chiral centres of natural Hyp **1**, through a sequence of steps is long, tedious, expensive and low yielding besides formation of an unwanted olefin by-product that further complicated the purification process as claimed by Stille.[16] Despite these limitations, this strategy is the only one that has been followed by other groups mostly for the synthesis of

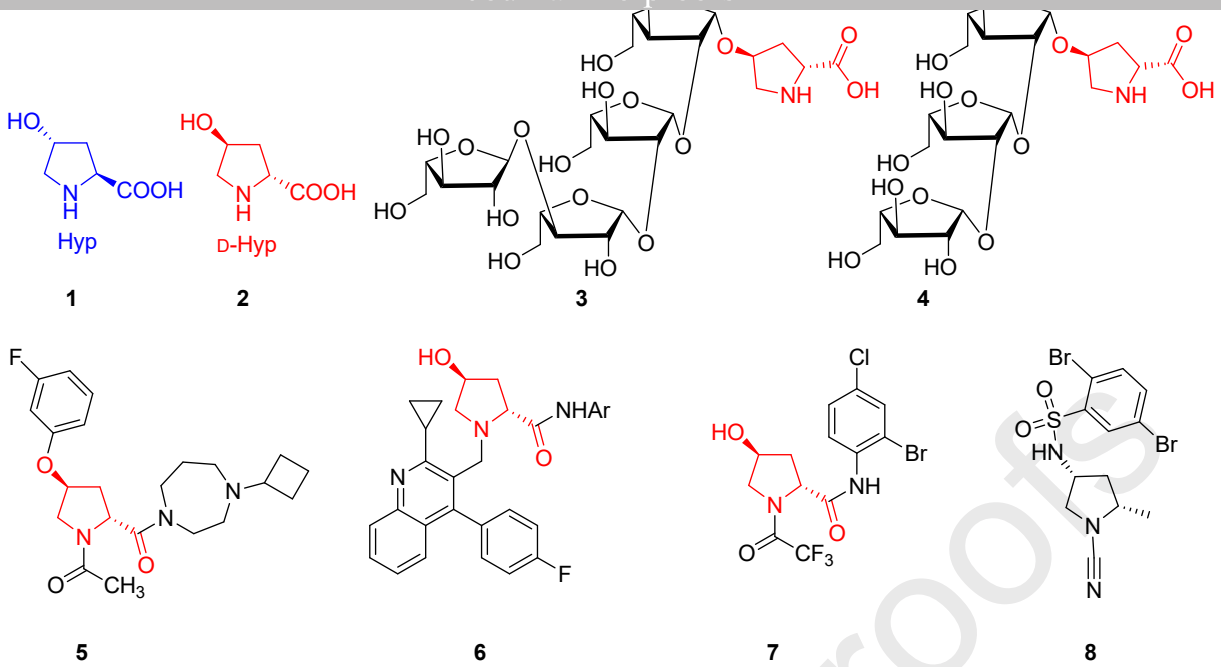


Figure 1. Structures of hydroxyl proline and relevant compounds of biological significance

protected D-Hyp and not D-Hyp itself.[4,11] Two other strategies reported by Arai[17] and Pilli[18] are synthetically not attractive as D-Hyp was obtained as one of the many possible products from mixtures.

Trans-4-hydroxy-D-prolinol **9**, the reduced form of D-Hyp **2**, also plays significant roles in the areas of synthetic organic chemistry and biology. Synthesis of biologically important pyrrolidine based nucleosides derived from *trans*-4-hydroxy-D-prolinol and its derivatives are known.[19] Constrained FTY720 analogue **10**, benzyl ether derivative of *trans*-4-hydroxy-D-prolinol, possess anticancer activity.[20] *Trans*-4-hydroxy-D-prolinol and its derivatives such as **11** have been successfully employed as chiral catalysts in various asymmetric synthesis[21] and receptor binding studies.[22] The only method available for *trans*-4-hydroxy-D-prolinol is through reduction of the ester of D-Hyp.

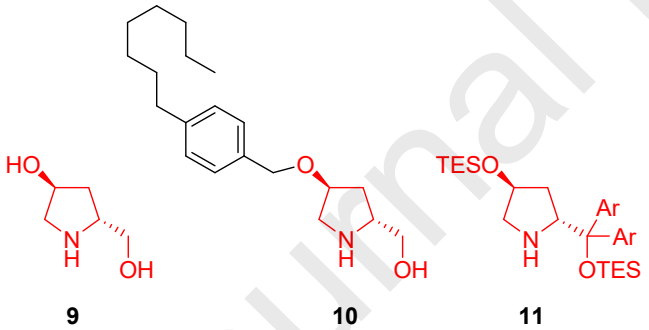
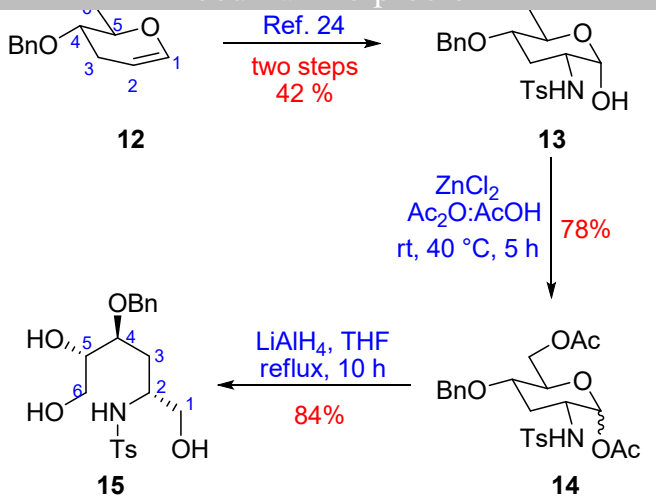


Figure 2. Structures of 4-hydroxy-D-prolinol and its derivatives.

Given this background and due to paucity of enough strategies to access D-Hyp and 4-hydroxy-D-prolinol, it was considered worthwhile to develop a new chiron based approach for the synthesis of both of them starting from a substrate that already possesses all the required absolute stereocentres and proceeds with complete stereochemical integrity.

Results and Discussion

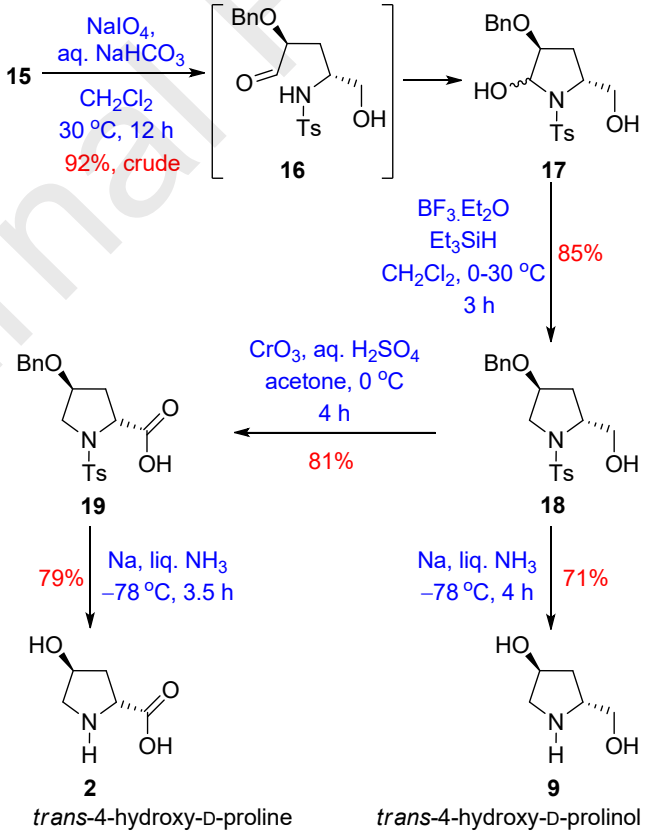
Recently, we have reported a divergent synthesis of 1,4-dideoxy-1,4-imino-L-xylitol and deacetyl (+)-anisomycin wherein their key pyrrolidine moiety was installed through an oxidative cleavage cum concomitant intramolecular cyclization of a vicinal diol derived from tri-*O*-benzyl-D-glucal.[23] It was envisaged that a similar reaction on 4,6-di-*O*-benzyl-3-deoxy-D-glucal **12**[24,25] derived vicinal diol would offer a straightforward approach to D-Hyp and its corresponding prolinol. With this idea, we started our synthesis with the chemoselective debenzylation of the primary benzyloxy group of hemiacetal **13**, which, in turn, was synthesized in one-pot two steps from 4,6-di-*O*-benzyl-3-deoxy-D-glucal **12** as reported by us earlier.[25] Exposure of hemiacetal **13** to $ZnCl_2$ in presence of Ac_2O and AcOH[26] resulted in a facile debenzylative acetolysis of primary benzylozy group that was also accompanied with acetylation of the anomeric hydroxyl group to give the diacetate **14** in 78% yield. Next, reduction of the acetate groups of **14** and in situ reductive ring opening of



Scheme 1. Synthesis of intermediate **15** from glucal **12**.

the resulting hemiacetal to triol **15** (84% yield) was accomplished by refluxing it with $LiAlH_4$ in THF (Scheme 1).

As planned, oxidative cleavage of vicinal diol group of **15** was then carried out with $NaIO_4$ in dichloromethane at 0 ºC–rt for 12 h. The reaction directly afforded a diastereomeric mixture of cyclic hemiaminal **17**, in 92% yield, formed through concomitant cyclization of the initially formed aldehyde **16**, as evidenced from the crude NMR (^1H and ^{13}C) spectra of the product. Absence of signal due to aldehydic proton and carbonyl carbon as well as appearance of a signal at δ 5.45 ppm (due to hemiaminal proton) and δ 88.24 ppm (due to hemiaminal carbon) in its ^1H and ^{13}C NMR spectra respectively confirmed the formation of pyrrolidine ring. The product was filtered through a short silica gel column and was taken forward for the next step as such. Deoxygenation of hemiaminal **17** was next performed with Et_3SiH in presence of $BF_3.Et_2O$ to get **18** in 85% yield. Oxidation of side chain primary hydroxyl group of **18** under Jones' condition (CrO_3, aq. H_2SO_4) smoothly delivered the corresponding carboxylic acid **19**. One step deprotection of both the benzyl and tosyl groups of **19** was conveniently achieved under Birch condition to obtain the target molecule, *trans*-4-hydroxy-D-proline, **2** in 79% yield (Scheme 2). Its specific rotation $[\alpha]^{29}_D$ +72.0 (*c* 1.0, H_2O) is in complete agreement with the literature reported values $[\alpha]^{25}_D$ +76.0 (*c* 2.0, H_2O)}[15] and {$[\alpha]^{21}_D$ +79.3 (*c* 2.0, H_2O)},[16] so also its ^1H and ^{13}C NMR spectral data.[18] On the other hand, direct Birch reduction on **18** afforded *trans*-4-hydroxy-D-prolinol **9** in 71% yield (Scheme 2).



Scheme 2. Synthesis of *trans*-4-hydroxy-D-proline and prolinol.

In conclusion, we have accomplished a practical synthesis of 4-hydroxy-D-proline and prolinol starting from 4,6-di-*O*-benzyl-3-deoxy-D-glucal through oxidative cleavage as the key step. The novelty of the work is that the whole synthetic sequence proceeds through complete stereochemical integrity. Notably, there was no formation of unwanted side products/mixtures in any of the steps. Synthesis of 4-hydroxy-D-proline has been accomplished in 11 steps from commercially available 3,4,6-tri-*O*-acetyl-D-glucal with an overall yield of 9.6%. It may be noted that the literature reliable method[16] to obtain 4-hydroxy-D-proline was carried out in 10 steps from *trans*-4-hydroxy-L-proline with an overall yield of 4.2% and required excess of expensive silver carbonate as well as hazardous diazomethane. As all the steps described herein are well established and also do not require any special reaction condition, this methodology should be easily amenable for scale up. This synthetic protocol is thus expected to serve as an attractive alternative to the existing ones for the synthesis of D-Hyp.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for financial support in the form of a research grant (02(243)/15/EMR-II) and a research fellowship to U.K.M. The authors also thank the Department of Science and Technology (DST) and the Indian Institute of Technology Delhi (IITD) for funding of the ESI-HRMS facility at IIT Delhi.

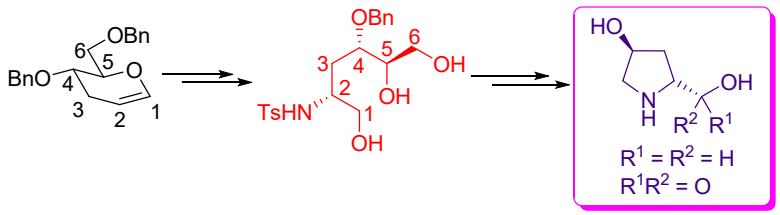
Appendix A. Supplementary data

Supplementary data (experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra of all new compounds) to this article can be found at https://doi.org/10.1016/j.tetlet.2020

References and notes

1. Gorres, K. L.; Raines, R. T. *Crit. Rev. Biochem. Mol. Biol.* **2010**, *45*, 106–124.
2. (a) Ramshaw, J. A. M.; Shah, N. K.; Brodsky, B. *J. Struct. Biol.* **1998**, *122*, 86-91. (b) McCaldon, P.; Argos, P. *Proteins* **1988**, *4*, 99–122. (c) White, C. E.; Gavina, J. M. A.; Morton, R.; Britz-McKibbin.; Finan, T. M. *Mol. Microbiol.* **2012**, *85*, 1133–1147. (d) Srivastava, A. K.; Khare, P.; Nagar, H. K.; Raghuwanshi, N.; Srivastava, R. *Curr. Prot. Pept. Sci.* **2016**, *17* 596–602.
3. Bollig, K.; Lamshöft, M.; Schweimer, K.; Marner, F. –J.; Budzikiewicz, H.; Waffenschmidt, S. *Carbohydr. Res.* **2007**, *342*, 2557–2566.
4. Zhu, K.; Yang, J. –S. *Tetrahedron* **2016**, *72*, 3113–3123.
5. Nishizawa, N.; Niida, A.; Adachi, Y.; Kanematsu-Yamaki, Y.; Masuda, Y.; Kumano, S.; Yokoyama, K.; Noguchi, Y.; Asakawa, T.; Hirabayashi, H.; Amano, N.; Takekawa, S.; Ohtaki, T.; Asami, T. *Bioorg. Med. Chem.* **2017**, *25*, 5718–5725.
6. Pippel, D. J.; Young, L. K.; Letavic, M. A.; Ly, K. S.; Naderi, B.; Soyode-Johnson, A.; Stocking, E. M.; Carruthers, N. I.; Mani, N. S. *J. Org. Chem.* **2010**, *75*, 4463–4471.
7. Ganesan, M. S.; Raja, K. K.; Narasimhan, K.; Murugesan, S.; Kumar, B. K. *J. Mol. Struct.* **2020**, *1208*, 127873.
8. Darehkordi, A.; Ramezani, M. *Mol. Divers.* **2017**, *21*, 305–315.
9. Williams, M. A.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3616–3625.
10. Vrieze, D. C. WO 200638119 2006.
11. Lowe, G.; Vilaivan, T. *J. Chem. Soc. Perkin Trans 1* **1997**, 539–546.
12. Kotian, P. L.; Babu, Y. S.; Kumar, V. S.; Zhang, W.; Vogeti, L. WO 2017/059178 A1.
13. Lainé, D.; Palovich, M.; McCleland, B.; Petitjean, E.; Delhom, I.; Xie, H.; Deng, J.; Lin, G.; Davis, R.; Jolit, A.; Nevins, N.; Zhao, B.; Villa, J.; Schneck, J.; McDevitt, P.; Midgett, R.; Kmett, C.; Umbrecht, S.; Peck, B.; Davis, A. B.; Bettoun, D. *ACS Med. Chem. Lett.* **2011**, *2*, 142–147.
14. (a) Hou, K. –Q.; Chen, X. –P.; Huang, Y.; Chan, A. S. C.; Luo, H. –B.; Xion, X. –F. *Org. Lett.* **2020**, *22*, 584–588.
15. Robinson, D. S.; Greenstein, J. P. *J. Biol. Chem.* **1952**, *195*, 383–388.
16. Baker, G. L.; Fritschel, S.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954–2960.
17. Krishnamurthy, S.; Arai, T.; Nakanishi, K.; Nishino, N. *RSC Advances* **2014**, *4*, 2482–2490.
18. Schuch, C. M.; Pilli, R. A. *Tetrahedron Asymmetry* **2002**, *13*, 1973–1980.
19. (a) Peterson, M. L.; Vince, R. J. Med. Chem. 1991, 34, 2787–2797. (b) Ng, K. –m. E.; Orgel, L. E. *J. Med. Chem.* **1989**, *32*, 1754–1757. (c), Nishonov, A. A.; Ma, X.; Nair, V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4099–4101.
20. Fransson, R.; McCracken, A. N.; Chen, B.; McMonigle, R. J.; Edinger, A. L.; Hanessian, S. *ACS Med. Chem. Lett.* **2013**, *4*, 969–973.
21. (a) Hou, K. –Q.; Chen, X. –P.; Huang, Y.; Chan, A. S. C.; Luo, H. –B.; Xiong, X. –F. *Org. Lett.* **2020**, *22*, 584–588.
22. Heindl, C.; Hübner, H.; Gmeiner, P. *Tetrahedron Asymmetry* **2003**, *14*, 3141–3152.
23. Harit, V. K.; Ramesh, N. G. *Carbohydr. Res.* **2020**, *492*, 107988.
24. 4,6-Di-*O*-benzyl-3-deoxy-D-glucal **12** was synthesized, in three steps, from commercially available tri-*O*-acetyl-D-glucal with an overall yield of 69.5% as per the procedure described in the following papers. (a) Clark, J. S.; Romiti, F.; Sieng, B.; Paterson, L. C.; Stewaart, A.; Chaudhury, S.; Thomas, L. H. *Org. Lett.* **2015**, *17*, 4694-4697. (b) Trost, B. M.; Rhee, Y. H. *Org. Lett.* **2004**, *23*, 4311-4313. (c) Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc.* **1970**, *92*, 6661-6663. (d) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C).* **1969**, 570-575.
25. Mishra, U. K.; Ramesh, N. G. *Carbohydr. Res.* **2020**, *489*, 107931 and references cited therein.
26. Frigell, J.; Pearcey, J. A.; Lowary, T. L.; Cumpstey, I. *Eur. J. Org. Chem.* **2011**, 1367–1375.

Graphical Abstract



HIGHLIGHTS

Trans-4-hydroxy-L-proline (Hyp) is a non-proteinogenic amino acid.

Trans-4-hydroxy-D-proline (D-Hyp) is a non-natural enantiomer of Hyp.

Hyp and D-Hyp have found various biological applications.

4,6-Di-*O*-benzyl-3-deoxy-D-glucal has been utilized to synthesize D-Hyp.

The reported synthetic protocol proceeds with complete stereochemical integrity.