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Synthesis of a Protected 3,4-Dihydroxyproline from a Pentose Sugar

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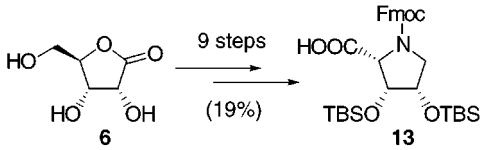
ABSTRACT



D-Ribonolactone (6) was transformed into *N*-((fluorenylmethoxy)carbonyl)-3,4-bis-*O*-(*tert*-butyldimethylsilyl)-D-2,3-*cis*-3,4-*cis*-3,4-dihydroxyproline (13) in nine chemical steps. This represents a potentially general strategy for the synthesis of 3,4-dihydroxyprolines, utilizing the pentose sugar series as starting materials.

3,4-Dihydroxyproline (DHP) contains the three stereogenic centers C2, C3, and C4; there are eight possible stereoisomers. Three members of the L-series have been isolated from natural sources.[1] The L-2,3-*cis*-3,4-*trans* isomer (**1**; Figure 1) was isolated from the cell wall hydrolysates of the diatom

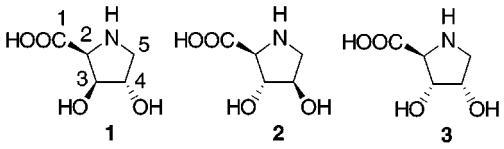


Figure 1. 3,4-Dihydroxyprolines from natural sources.

Navicula pelicullosa almost 30 years ago.[2] In 1980, the L-2,3-*trans*-3,4-*trans* isomer (**2**) was isolated from the acid hydrolysates of the toxic mushroom *Amanita virosa*.[3] In 1994, the L-2,3-*trans*-3,4-*cis* isomer **3** was identified as the sixth residue in the repeating decapeptide sequence of Mefp1, an adhesive protein produced by the marine mussel *Mytilus edulis*.[4]

Interest in these molecules, and related pyrrolidines, stems largely from their ability to inhibit glycosidase enzymes.[5] Our focus, however, is on the role of dihydroxyprolines in peptide structure and function. To properly investigate structure−activity relationships (SARs), we required an efficient synthesis of DHP, which would afford access to all stereoisomers.

All eight stereoisomers, or related aza sugars, have been synthesized previously.[6] As a synthetic target, DHP is deceptively challenging: although a small molecule, it is densely functionalized and rich in stereochemistry. Previous synthetic strategies can be divided broadly into two groups:

(1) Mauger, A. B. *J. Nat. Prod.* **1996**, *59*, 1205−1211.
(2) Nakajima, T.; Volcani, B. E. *Science* **1969**, *164*, 1400−1401.
(3) Buku, A.; Faulstich, H.; Wieland, T.; Dabrowski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2370−2371.
(4) Taylor, S. W.; Waite, J. H.; Ross, M. M.; Shabanowitz, J.; Hunt, D. G. *J. Am. Chem. Soc.* **1994**, *116*, 10803−10804.
(5) (a) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340−347. (b) Sears, P.; Wong, C. H. *Chem. Commun.* **1998**, 1161−1170. (c) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171−1202.
(6) For some recent examples, with comprehensive references to earlier work, see: (a) Huang, Y.; Dalton, D. R.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 372−376. (b) Pohlit, A. M.; Correia, C. R. D. *Heterocycles* **1997**, *45*, 2321−2325. (c) Schumacher, K. K.; Jiang, J.; Joullié, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 45−53. (d) Deming, T. J.; Fournier, M. J.; Mason, T. L.; Tirrell, D. A. *J. Macromol. Sci. Pure Appl. Chem.* **1997**, *A34*, 2143−2150. (e) Defoin, A.; Sifferlen, T.; Streith, J. *Synlett* **1997**, 1294−1296. (f) Zanardi, F.; Battistini, L.; Nespi, M.; Rassu, G.; Spanu, P.; Cornia, M.; Casiraghi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1167−1180.

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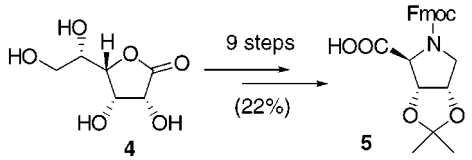
those which lead to DHP's with 3,4-*cis* relative stereochemistry and those which culminate in a 3,4-*trans* arrangement of hydroxy groups. Our mandate was to devise a reaction sequence which would permit the stereospecific synthesis of each isomer.

We have recently reported a synthesis of an L-2,3-*trans*-3,4-*cis*-DHP (**5**) from D-gulonolactone (**4**; Scheme 1)[7] by

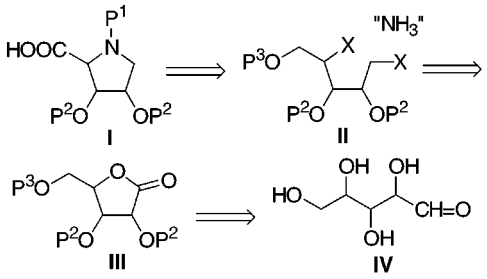
Scheme 1



adapting the methodology of Fleet et al.[8] This first-generation approach has two drawbacks: it involves the excision of one carbon atom with concomitant destruction of a stereogenic center, and the use of an acetonide (or indeed, any cyclic protecting group) limits the strategy to DHP's with a 3,4-*cis* relative stereochemistry.

To overcome these limitations, we decided to use the pentose family of sugars as our source of chirality. Protection of the 1,2-diol required the use of "independent" protecting groups for each secondary alcohol. Our retrosynthetic analysis, as outlined in Scheme 2, does not specify stereo-

Scheme 2



chemistry intentionally. We believe that the disconnections apply regardless. P^1, P^2, and P^3 are protecting groups. Pyrrolidine **I** can be envisaged to arise from the suitably functionalized precursor **II**, using the double-displacement chemistry of Fleet. Compound **II** can be derived from appropriately protected γ-lactone **III** via a reductive ring opening. Lactones of general structure **III** ($P^2 = P^3 = H$) can be obtained by bromine oxidation of aldopentoses,[9] represented by the generic structure **IV**.

By selection of the appropriate pentose sugar (Table 1), it ought to be possible to prepare any isomer of DHP.

Table 1. Dihydroxyprolines from Pentoses

DHP isomer	pentose precursor
L-2,3-*cis*-3,4-*cis*	L-ribose
L-2,3-*cis*-3,4-*trans*	L-arabinose
L-2,3-*trans*-3,4-*cis*	L-lyxose
L-2,3-*trans*-3,4-*trans*	L-xylose
D-2,3-*cis*-3,4-*cis*	D-ribose
D-2,3-*cis*-3,4-*trans*	D-arabinose
D-2,3-*trans*-3,4-*cis*	D-lyxose
D-2,3-*trans*-3,4-*trans*	D-xylose

We chose D-2,3-*cis*-3,4-*cis*-DHP as our test case, because D-ribonolactone is commercially available. The synthesis of protected amino acid **13** is outlined in Scheme 3.[10] The primary alcohol of compound **6** was protected as its triphenylmethyl (trityl) ether.[11] Formation of *tert*-butyldimethylsilyl ethers from the two secondary alcohols, at C2 and C3, was accomplished under standard conditions[12] to give **7**.

Fleet and Son have previously reported that reductive opening of silyl-protected hydroxylactones with $LiAlH_4$ can be accompanied by silyl migration.[12b] On the basis of their experience, we employed $LiBH_4$, which effected reduction slowly but cleanly to give compound **8** as the sole product.

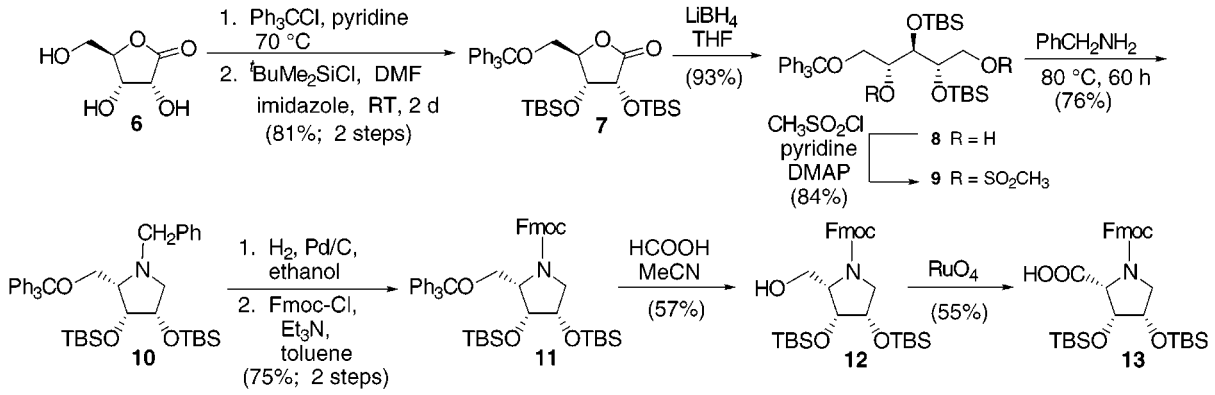
Diol **8** was converted to bis(mesylate) **9** by adding a solution of the diol in pyridine, dropwise, to a premixed solution of methanesulfonyl chloride and catalytic DMAP in pyridine. Heating bis(mesylate) **9** in neat benzylamine (1.5 mL of benzylamine/g of substrate), at 80 °C for 60 h, led to formation of pyrrolidine **10**.

Replacement of the *N*-benzyl substituent by the Fmoc group (Fmoc = (fluorenylmethoxy)carbonyl) was performed for two reasons: to increase stabilility toward oxidation (vide supra) and to provide a suitable protecting group for downstream applications in peptide chemistry. Hydrogenolysis of **10** gave the corresponding secondary amine. Significantly, the trityl group was stable to these reaction conditions.[13] The crude amine was treated directly with fluorenylmethyl chloroformate in toluene to give **11** in an efficient manner.

Bessodes et al. had previously reported the selective cleavage of a trityl ether in the presence of *tert*-butyldi-

(7) Weir, C. A.; Taylor, C. M. *J. Org. Chem.* **1999**, *64*, 1554−1558.
(8) Fleet, G. W. J.; Son, J. C.; Green, D. St. C.; di Bello, I. C.; Winchester, B. *Tetrahedron* **1988**, *44*, 2649−2655.
(9) See: (a) Bouchez, V.; Stasik, I.; Beaupère, D.; Uzan, R. *Carbohydr. Res.* **1997**, *300*, 139−143. (b) Han, S. Y.; Joullié, M. M.; Fokin, V. V.; Petasis, N. A. *Tetrahedron: Asymmetry* **1994**, *5*, 2535−2562 and references therein.
(10) All new compounds in Scheme 3 gave satisfactory ^1H and ^{13}C NMR and HRMS data.
(11) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988−2006.
(12) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991; Chapter 2, p 77. (b) Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637−2647.
(13) Hydrogenolysis of trityl ethers has been reported: Mirrington, R. N.; Schmalzl, K. J. *J. Org. Chem.* **1972**, *37*, 2877−2881. However, others have described the selective cleavage of a benzylamine in the presence of a trityl ether: Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3827−3840.

Scheme 3



methylsilyl ethers.[14] These reaction conditions (25% v/v formic acid in acetonitrile) proved to be too harsh for substrate **11**; ^{1}H NMR and HRMS analysis of the major product indicated that only a single TBS group remained in the molecule. Fortunately, by reducing the amount of formic acid (to 7% v/v in acetonitrile), it was possible to obtain primary alcohol **12** (57% yield), accompanied by a 40% recovery of **11**. This represents a 97% yield, based on recovered starting material. Compound **12** was oxidized to acid **13**[15] using ruthenium tetroxide (generated in situ from $NaIO_4$ (4.1 equiv) and $RuCl_3 \cdot xH_2O$ (0.022 mol %) in MeCN/CCl_4/H_2O (1.0:1.0:1.5 ratio by volume)).

In conclusion, we have executed an effective and efficient synthesis of *N*-((fluorenylmethoxy)carbonyl)-3,4-bis-*O*-(*tert*-butyldimethylsilyl)-D-2,3-*cis*-3,4-*cis*-DHP (**13**). The reaction sequence is composed of nine steps and proceeds in an overall yield of 19%. We hope that the reaction chemistry presented herein can be applied to the synthesis of other stereoisomers of 3,4-dihydroxyproline. This is currently under investigation and will be reported in due course.

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(14) Bessodes, M.; Komiotis, D.; Antonakis, K. *Tetrahedron Lett.* **1986**, *27*, 579−580.

(15) Compound **13** was obtained as a colorless oil: R_f 0.54 (1:1 hexanes−EtOAc); $[\alpha]^{20}_D = +13.1°$ (c = 0.70, $CHCl_3$). Mixture of rotamers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.18 (s, 6H), 0.88 (s, 18H), 3.42−3.54 (m, 1.5H), 3.62−3.70 (m, 0.5 H), 4.12−4.17 (m, 1H), 4.25 (t, J = 6.8 Hz, 2H), 4.37−4.42 (m, 3H), 7.31 (t, J = 7.1 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.51−7.60 (m, 1H), 7.74 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.8, 18.2, 25.6, 25.8, 46.9, 51.9 & 52.6, 62.9, 67.6 & 68.7, 72.9 & 73.2, 73.7, 119.9, 125.2, 125.6, 127.1, 127.7, 141.3, 155.2 & 155.3, 168.6. HRMS (CI$^+$): calcd for $C_{32}H_{48}NO_6Si_2$ $(M + H)^+$, 598.3020; found, 598.3022.