ORGANIC LETTERS

1999
Vol. 1, No. 5
787−789

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

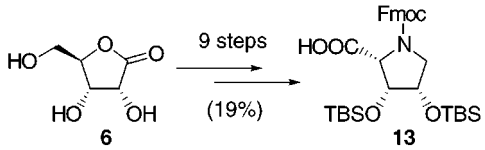
Claudette A. Weir and Carol M. Taylor*

Department of Chemistry, University of Auckland, Private Bag 92019, Auckland, New Zealand

cm.taylor@auckland.ac.nz

Received June 24, 1999

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

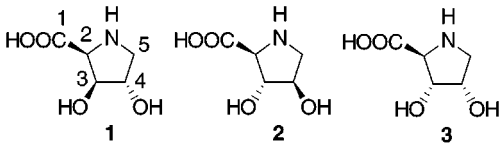


Figure 1. 3,4-Dihydroxyprolines from natural sources.

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:

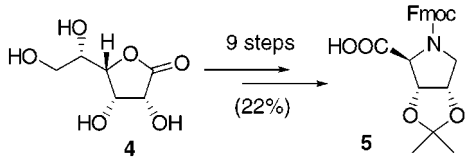
(1) Mauger, A. B. *J. Nat. Prod.* **1996**, *59*, 1205−1211.
(2) Nakajima, T.; Volcani, B. E. *Science* **1969**, *164*, 1400−1401.
(3) Buku, A.; Faulstich, H.; Wieland, T.; Dabrowski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2370−2371.
(4) Taylor, S. W.; Waite, J. H.; Ross, M. M.; Shabanowitz, 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.

10.1021/ol990763v CCC: $18.00
Published on Web 07/30/1999

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

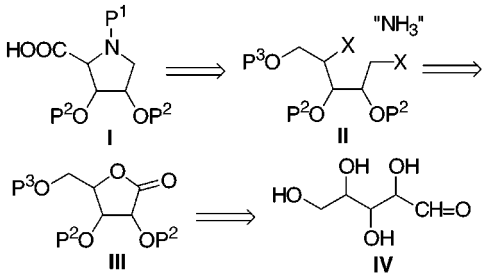
Scheme 1



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.

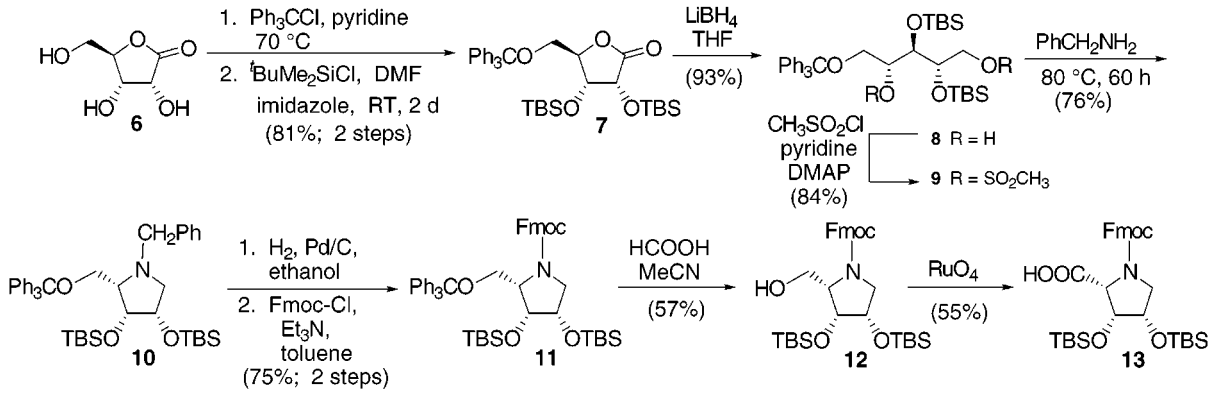
Diol **8** was converted to bis(mesylate) **9** by adding a solution of the diol in pyridine, dropwise, to a premixed solution of methanesulfonyl chloride and catalytic DMAP in pyridine. Heating bis(mesylate) **9** in neat benzylamine (1.5 mL of benzylamine/g of substrate), at 80 °C for 60 h, led to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

Acknowledgment. We thank the Marsden Fund (Grant 96-UOA-617), administered by the Royal Society of New Zealand, for financial support. We thank Michael F. Walker for running mass spectrometry experiments and for maintenance of the NMR facility at the University of Auckland.

OL990763V

(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.