Synthesis of a Novel Tetrahydroxylated β-Homoproline

Armin Benz, Francesca Cardona,* Andrea Goti*

Dipartimento di Chimica 'Ugo Schiff', HeteroBioLab, Università di Firenze, associated with INSTM and ICCOM-C.N.R., Via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy
Fax +39(055)4573531; E-mail: andrea.goti@unifi.it; E-mail: francesca.cardona@unifi.it

Received 22 October 2010

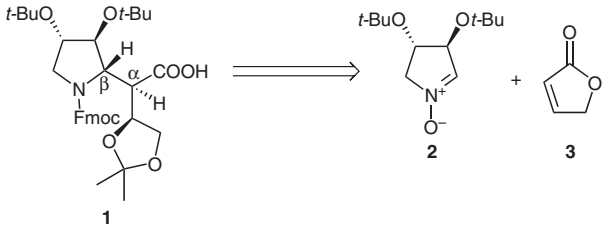
Dedicated to Prof. Alberto Brandi on the occasion of his 60th birthday

Abstract: A gram-scale synthesis of a novel densely functionalized and orthogonally protected β-homoproline was achieved from L-tartaric acid derived nitrone through a highly stereoselective 1,3-dipolar cycloaddition to γ-crotonolactone as the key initial step, followed by appropriate elaboration of the adduct.

Key words: non-natural amino acid, total synthesis, nitrone, cycloaddition

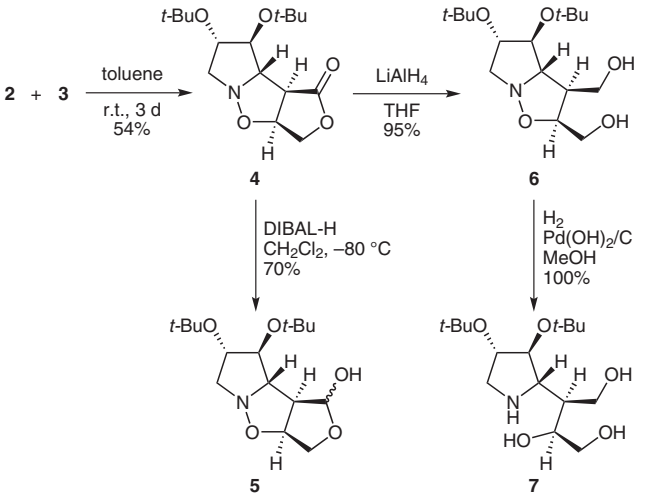
The importance of β-amino acids is related to their role as synthetic intermediates[1] and as components of biologically relevant compounds including peptidomimetics[2] and β-peptides.[3,4] However, among these synthetic peptidomimetics, β-homoproline derivatives have been scarcely investigated, apart from a recent example in which the incorporation of a new cyclic β-amino acid into a simple tripeptide has been evaluated.[5] Moreover, some sulfonamide derivatives of β-homoproline have been recently studied as organocatalysts for Michael and aldol reactions.[6]

We present in this Letter a straightforward gram-scale synthesis of a novel β-homoproline **1** that is hydroxylated on the pyrrolidine skeleton as well as on the chain at the α-carbon, by means of a highly selective 1,3-dipolar cycloaddition of L-tartaric acid derived nitrone **2** to γ-crotonolactone (**3**) as the first key step, required for the highly selective installation of three new stereocenters on the target molecule (Scheme 1).



Scheme 1 Retrosynthetic analysis for β-homoproline **1**

Cycloaddition of nitrone **2**[7] to γ-crotonolactone (**3**) proceeded smoothly in toluene at room temperature (Scheme 2), affording a crude mixture (89%) of two cycloadducts,[8] from which the major *exo-anti* adduct **4** was isolated in 54% yield after recrystallization from hexanes.[9] The stereoselectivity of this reaction has been thoroughly investigated by Chmielewski and co-workers,[8a] who demonstrated that the minor adduct (the two diastereomers are obtained in 93:7 ratio) derives from an *exo-syn* approach, since the *tert*-butoxy group at C-4 on nitrone **2** eliminates the possibility of *endo* adducts, which are indeed observed with L-malic acid derived nitrone (that bears only one vicinal *tert*-butoxy group).[8a,10] Formation of this minor adduct in only minute amount (<10%) is significant, since the desired major adduct can be recovered pure in bulk amounts by a simple recrystallization procedure, without the need of more expensive and time-consuming separation procedures. Among the solvents tested, hexanes performed best for the crystallization of pure adduct **4**.

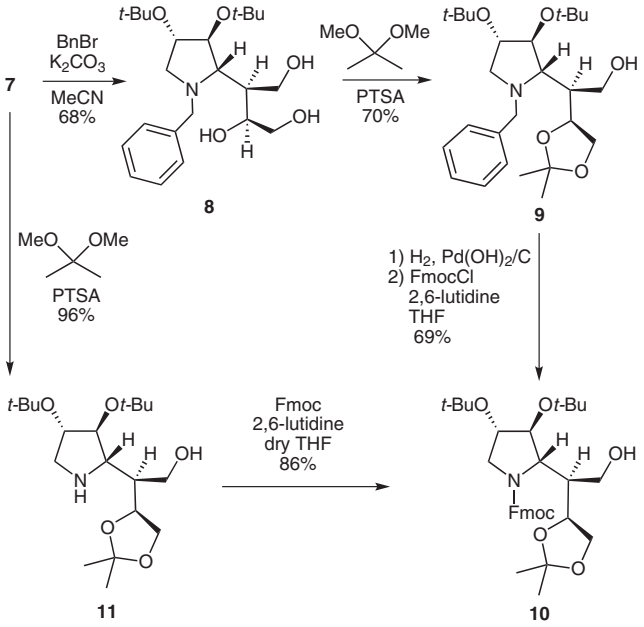


Scheme 2 Cycloaddition reaction, reduction of the lactone moiety, and N–O bond cleavage

Reductive cleavage of the N–O bond performed on compound **4**, attempted in several reaction conditions, always failed. Hydrogenolysis catalyzed by $Pd(OH)_2/C$ gave a complex mixture and treatment with $Mo(CO)_6$ in MeCN–H_2O[11] led to unaltered starting material. On treatment of **4** with Zn in AcOH–H_2O[12] a major product was isolated which derived from elimination of water from the expected γ-amino alcohol leading to the corresponding α,β-unsaturated lactone. We turned then our attention to stronger reducing agents, namely aluminium hydrides, anticipating that the lactone functionality might be more reactive than

SYNLETT 2011, No. 2, pp 0231–0234
Advanced online publication: 04.01.2011
DOI: 10.1055/s-0030-1259293; Art ID: G31310ST

the N–O bond towards these reagents. Indeed, treatment with DIBAL-H gave the reduced lactol **5** in 70% yield (Scheme 2), but N–O bond cleavage through hydrogenolysis catalyzed by $Pd(OH)_2/C$ was unsuccessful even at this level,[13] leaving the unaltered lactol **5**. In order not to lose the stereochemical information at the α-carbon, we then decided to reduce the lactone double bond to the corresponding alcohol. Treatment of **4** with $LiAlH_4$ in THF gave pure **6**[14] in 95% yield. To our delight, subsequent hydrogenolysis catalyzed by $Pd(OH)_2/C$ afforded the polyhydroxypyrrolidine **7** in quantitative yield (Scheme 2). Protection of the amine moiety as Fmoc derivative (commonly used in peptide synthesis) was attempted at this stage, by treating **7** with FmocCl and 2,6-lutidine in dry THF, but only 30% of the desired product was obtained. Since such a low yield at this early stage was not acceptable for a large-scale synthesis of the desired β-homoproline **1**, we decided to temporarily protect the nitrogen atom as benzyl derivative, by reaction with BnBr in MeCN in the presence of an excess of K_2CO_3, affording compound **8** in 68% yield (Scheme 3).

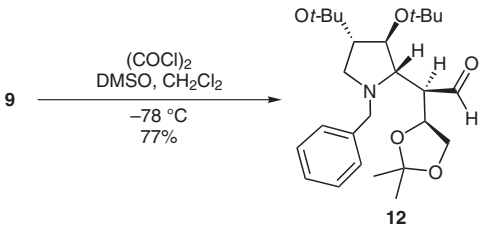


Scheme 3 Alternative syntheses of alcohol **10**

Selective protection of the 1,2-diol over the 1,3-diol on compound **8** was attempted using several reaction conditions. Reaction in acetone with *p*-toluenesulfonic acid (PTSA) catalysis (0.1 equiv) gave no reaction, while treatment with iodine (0.2 equiv) in acetone afforded a complex mixture of products. Finally, reaction with dimethoxypropane as solvent in the presence of 1.2 equivalents of PTSA gave **9** in 70% yield. Clearly, the first equivalent of PTSA formed the pyrrolidinium salt, while the remaining 0.2 equivalents catalyzed the protection reaction.

Subsequent hydrogenolysis catalyzed by $Pd(OH)_2/C$, followed by protection as Fmoc derivative afforded **10** in 69% yield over two steps (and 32% yield over four steps from **7**, Scheme 3). Having found the optimized conditions for the selective protection of the 1,2-diol moiety which involved formation of an ammonium salt, we envisaged that this procedure might be also amenable to direct application on the amine **7**, thus reducing considerably the synthetic steps. Indeed, direct protection of compound **7** with dimethoxypropane as solvent in the presence of 1.2 equivalents of PTSA afforded compound **11** in excellent yield (96%) on gram scale. The following protection of the nitrogen atom as Fmoc derivative gave pure **10** in 86% yield (82% yield over two steps), thus establishing a straightforward two-step synthesis of **10** from triol **7** (Scheme 3).

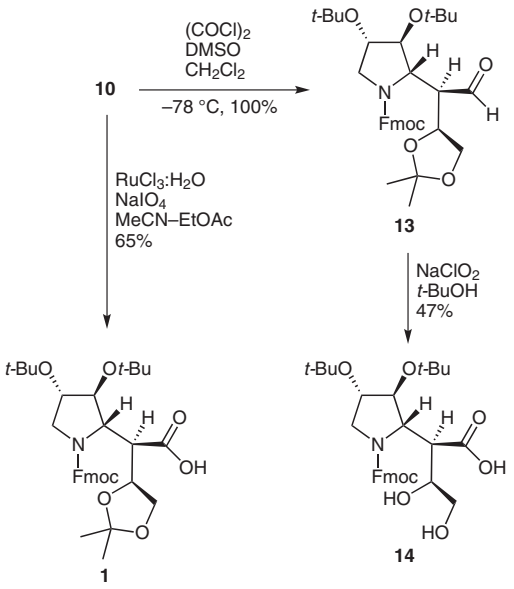
The final key oxidation step of the unprotected primary alcohol was attempted on benzyl-protected pyrrolidine **9** as well as on the Fmoc-protected **10**. This transformation turned out to be extremely challenging and led us to investigate both the direct conversion to carboxylic acid and the two-step conversion passing through the aldehyde intermediate.



Scheme 4 Oxidation of alcohol **9**

When the alcohol **9** was treated with Jones reagent (2.4 equiv) or $NaClO_2/NaOCl$ in combination with TEMPO as catalyst[15] the starting material was recovered unchanged. On the contrary an excess of Jones reagent, PCC, Dess–Martin reagent,[16] or $RuO_2 \cdot H_2O$ in combination with $NaIO_4$[17] all afforded complex mixtures of products. Eventually, oxidation of **9** to aldehyde **12** was achieved with TPAP/NMO catalytic system,[18] or with Swern oxidation[19] (Scheme 4), but **12** proved to be unstable to purification by flash column chromatography. An attempt to oxidize directly crude **12** with $KMnO_4$ in *t*-BuOH in the presence of NaH_2PO_4[20] afforded a complex mixture of products. Oxidation reactions of alcohol **10** gave some better results. A first attempt by exposing **10** to 0.02 equivalents of TEMPO and 3 equivalents of trichloroisocyanuric acid (TCCA) gave mainly the corresponding aldehyde **13** instead of the expected carboxylic acid,[21] which was more cleanly obtained by Swern oxidation (Scheme 5). Treatment of aldehyde **13** with $NaClO_2$ in a *t*-BuOH–MeCN solution buffered with aqueous NaH_2PO_4[22] occurred successfully but with concomitant deprotection of the acetonide moiety to furnish moderate yields of the acid **14**. This unsatisfying result showed nonetheless that the *tert*-butyl ether and acetonide protections can be considered orthogonal to some extent, the latter being deprotected under much milder conditions.

Finally, direct oxidation of alcohol **10** with RuO_4 catalyst formed in situ by reaction of catalytic ruthenium trichloride with stoichiometric sodium periodate[17] afforded the desired acid **1** in 65% yield.



Scheme 5 Oxidation of alcohol **10**; synthesis of β-homoproline **1**

In conclusion, we achieved a gram-scale straightforward synthesis of β-homoproline **1**[23] from L-tartaric acid derived nitrone **2** in six steps and 28% overall yield (80% average on the single steps). It is also worth to be noted that starting from readily available D-tartaric acid derived nitrone *ent*-**2**, the total synthesis of *ent*-**1** might be easily accessed.

Work is under way to investigate the conformational properties of the non-natural amino acid β-homoproline **1** in oligopeptides.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank Ente Cassa di Risparmio di Firenze (CRF), Italy and MIUR (PRIN 2008) for financial support. We also thank Dr Gianluca Soldaini for supervision of the work of AB. Brunella Innocenti and Maurizio Passaponti for technical assistance.

References and Notes

(1) For some recent reviews on β-amino acids, see: (a) Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Grošelj, U.; Zass, E. *Synthesis* **2009**, 1. (b) Kiss, L.; Fülöp, F. *Synlett* **2010**, 1302. (c) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *5*, 1656.

(2) (a) Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M. I. *Curr. Med. Chem.* **2002**, *9*, 811. (b) Porter, E. A.; Wang, X. F.; Lee, H. S.; Weisblum, B.; Gellman, S. H. *Nature (London)* **2000**, *404*, 565.

(3) (a) Seebach, D.; Abele, S.; Sifferlen, T.; Hängi, M.; Gruner, S.; Seiler, P. *Helv. Chim. Acta* **1998**, *81*, 2218. (b) Abele, S.; Vögtli, K.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1539.

(4) For some reviews on β-peptides, see: (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (c) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905. (d) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (e) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366. (f) Seebach, D.; Hook, D. F.; Glattli, A. *Biopolymers* **2006**, *84*, 23.

(5) Cordero, F. M.; Salvati, M.; Vurchio, C.; de Meijere, A.; Brandi, A. *J. Org. Chem.* **2009**, *74*, 4225.

(6) Tsandi, A.; Kokotos, C. G.; Kousidou, S.; Ragoussis, V.; Kokotos, G. *Tetrahedron* **2009**, *65*, 1444.

(7) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274.

(8) (a) Stecko, S.; Paśniczek, K.; Jurczak, M.; Urbańczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron: Asymmetry* **2006**, *17*, 68. (b) Goti, A.; Cicchi, S.; Cordero, F. M.; Fedi, V.; Brandi, A. *Molecules* **1999**, *4*, 1.

(9) For a comprehensive discussion of the possible approaches in cycloadditions to this class of nitrones, see: Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808; see also ref. 8b.

(10) For recent DFT studies of 1,3-dipolar cycloadditions of cyclic nitrones to unsaturated γ-lactones, see: (a) Stecko, S.; Paśniczek, K.; Michel, C.; Milet, A.; Pérez, S.; Chmielewski, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1660. (b) Stecko, S.; Paśniczek, K.; Michel, C.; Milet, A.; Pérez, S.; Chmielewski, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2140.

(11) (a) Cicchi, A.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351. (b) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633.

(12) (a) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315. (b) Cardona, F.; Parmeggiani, C.; Faggi, E.; Bonaccini, C.; Gratteri, P.; Sim, L.; Gloster, T. M.; Roberts, S.; Davies, G. J.; Rose, D. R.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 1627.

(13) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266.

(14) Stecko, S.; Jurczak, M.; Urbańczyk-Lipkowska, Z.; Solecka, J.; Chmielewski, M. *Carbohydr. Res.* **2008**, *343*, 2215.

(15) Zhao, M.; Eiichi Mano, J. L.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.

(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(17) For a review on RuO_4-catalyzed oxidations, see: Plietker, B. *Synthesis* **2005**, 2453.

(18) (a) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1993**, 433.

(19) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(20) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

(21) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999.

(22) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1171.

(23) **Data for Compound 1 (Mixture of Two Rotamers)** Yellow solid, mp 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.78 (m, 2 H), 7.68–7.60 (m, 2 H), 7.44–7.30 (m, 4 H), 4.70–4.66 (m), 4.61–4.24 (m), 4.01–3.97 (m), 3.92–3.81 (m), 3.73–3.64 (m), 3.42 (t, *J* = 9.5 Hz), 3.32 (t, *J* = 10.0 Hz), 3.26 (d, *J* = 11.5 Hz), 3.10 (d, *J* = 11.5 Hz) (for a total of 12 H), 1.40 (s), 1.33 (s), 1.32 (s), 1.29 (s) (for a total of 6 H), 1.25 (s), 1.20 (s), 1.18 (s), 1.08 (s) (for a total of 18 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.9, 176.8 (s, COOH), 156.4,155.1 (s, C=O Fmoc), 143.9, 143.8, 143.6, 141.4, 141.3, 141.2 (s, 4 C, Fmoc), 127.7–119.9 (d, 8 C, Fmoc), 108.3, 108.2 (s, CO acetonide), 78.4, 77.6, 76.3, 75.6, 75.5, 75.2 (d, 3 C), 74.7, 74.5, 74.4, 74.3 (s, 2 C, CO *t*-Bu), 68.1, 67.9, 67.5, 67.1 (t), 65.2, 64.5 (d), 54.6, 54.2 (t), 52.9, 51.7 (d), 47.1, 47.0 (d, Fmoc), 28.3, 28.2, 28.1, 28.0 (q, 6 C, *t*-Bu), 26.5, 26.3, 25.7, 25.5 (q, 2 C, acetonide). IR (KBr): 3600–2400 (large), 2976, 1706, 1368, 1185, 740 cm^{-1}. ESI-MS: *m/z* (%) = 596.25 (27)[M^+ + 1], 618.42 (100) [M^+ + Na]. Anal. Calcd for $C_{34}H_{45}NO_8$ (595.72): C, 68.55; H, 7.61; N, 2.35. Found: C, 68.32; H, 7.47; N, 2.68. $[\alpha]_D^{25}$ +3.27 (*c* 1.47, CH_2Cl_2).