Pergamon

Tetrahedron Letters, Vol. 35, No. 50, pp. 9359-9362, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02085-X

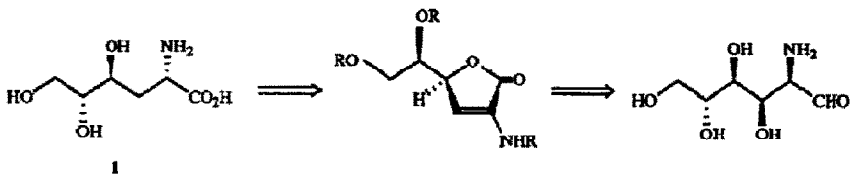
A Short Synthesis of (2S,4S,5R)-4,5,6-Trihydroxynorleucine.

Oscar Varela*, Alejandro P. Nin and Rosa M. de Lederkremer.

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires. Ciudad Universitaria. Pabellón II, 1428, Buenos Aires, Argentina.

Abstract: A direct synthesis of enantiomerically pure (2S,4S,5R)-4,5,6-trihydroxynorleucine (**1**) from a carbohydrate precursor (D-glucosamine), is described. D-glucosamine was oxidized to 2-amino-2-deoxy-D-gluconic acid (**2**), which was converted into the 2-acylamido-hex-2-enono-1,4-(**3**, **4**) and 1,5-lactone (**5**, **6**, **11**) derivatives. The hydrogenation of the enamine system of these compounds took place with excellent diastereofacial selectivity leading to the corresponding 3-deoxy-D-*arabino*-lactone derivatives (**7**-**10**, **12**, **13**). On *N*-deacetylation with HCl the hydrochloride derivative of **1**, in its 1,4-lactone form, was obtained with 57% overall yield, from **2**. The ammonium salt of **1** was also prepared.

Aliphatic and cyclic hydroxy-α-amino acids are of interest as antimetabolites and enzyme inhibitors. They occur naturally in free form like in seeds, fruits, microorganisms, seaweed, etc., or combined, taking part of large molecules, such as peptides and antibiotics.[1] Therefore, the synthesis of optically pure, modified amino acids constitutes an area of current intensive investigation.[2] Several synthetic strategies have employed carbohydrates as convenient starting materials.[3] Particularly, for the synthesis of hydroxyamino acids, aldonolactones and their derivatives have been widely used as a source of chiral carbons.[4] Thus, Vekemans *et al.*[5] reported a sequence which leads to enantiomerically pure trihydroxylated norleucines from L-gulono, D-mannono, and D-galactono-1,4-lactones. In this route the amino function is introduced by nucleophilic substitution of the sulfonylated hydroxyl group at C-2 of the sugar lactone by azide, followed by reduction. We have recently described[6] a diastereoselective synthesis of *cis*-4-hydroxypipecolic acid, *via* a diunsaturated aldonolactone precursor, which was obtained by high temperature acetylation of 2-amino-2-deoxy-D-gluconic acid (**2**). Also an unsaturated lactone (Scheme 1) could be the key intermediate for the synthesis of enantiomerically pure (2S,4S,5R)-4,5,6-trihydroxynorleucine (**1**). Such an intermediate could be obtained from D-glucosaminic acid (**2**), which can be readily prepared and in multigram scale, by mercury(II) oxide oxidation of D-glucosamine.[7]



Scheme 1

The advantage of our strategy is that the amino group is properly located in the starting sugar, avoiding the HO-2 derivatization, substitution and reduction steps. Furthermore, the sequence depicted in Scheme 1 would involve a hydrogenation which is expected to occur with inversion of the C-2 configuration,[6,8,9] leading to an amino acid of the L-series, generally found in nature. Therefore, we have explored the selectivity for the hydrogenation of the enono-1,4- and 1,5-lactones **3-6**, **11**, as the key step for the synthesis of **1**.

The furanones **3** and **4**, and the pyranones **5** and **6** were obtained on acylation of **2**, as previously reported,[8] with the following yields: **3**, 21%; **4**, 33%; **5**, 40% and **6**, 52%. The enamine system of the enonolactones **3-6** was hydrogenated at 15-30 psi, using 10% Pd/C as catalyst. For example, compound **3** (0.10 g, 0.35 mmol) dissolved in ethyl acetate (7 mL) was hydrogenated at 15 psi and room temperature, in the presence of 10% Pd/C (20 mg). After 4 h, the catalyst was filtered and the filtrate concentrated, to afford analytically pure,[10] syrupy **7** (98 mg, 98 % yield), having $[\alpha]_D$ +82°. Similarly, hydrogenation of **4** led to crystalline **8** (97% yield), mp 205° C, $[\alpha]_D$ -5.3°. As observed for analogous 2-*O*-substituted 3-deoxy-1,4-lactones,[9] and in agreement with the earlier described elucidation of the geometry of 3-deoxy-2,4-disubstituted-1,4-lactones,[9d] the large values for the coupling constants (table 1) between H-3,3' with H-2 and H-4, indicate a D-*arabino* configuration for **7** and **8**. A 2-azido analog of these compounds having opposite configuration at C-2 (D-*ribo*) showed[5] $J_{3,4}$ 8.5 Hz and $J_{3',4}$ 3.5 Hz. The excellent diastereoselectivity found for the hydrogenation of **3** and **4** may be attributed to the steric hindrance of the lateral chain at C-4, which will induce the approach of hydrogen from the opposite face of the molecule, regenerating the chiral center at C-2 with the desired *S*-configuration (L-amino acid).

Hydrogenation of the enono-1,5-lactones **5** and **6** was also performed under the conditions described for the furanones. The 3-deoxylactones **9** and **10** were respectively obtained from **5** and **6** with almost quantitative yields. Syrupy **9** gave $[\alpha]_D$ +132°, whereas **10** crystallized from ethanol, mp 158-160 °C, $[\alpha]_D$ +43°. Also in these cases, the hydrogenation took place with remarkable diastereofacial selectivity. The ^{1}H-NMR spectra

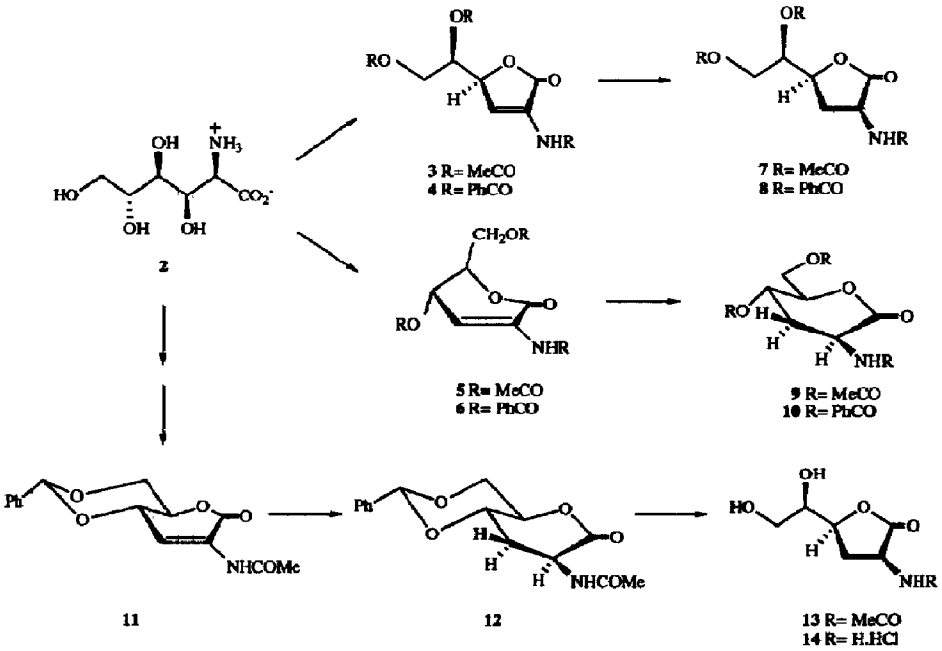


Table 1. ^{1}H-NMR Data for Compounds **1**, **7-10** and **12-14**.

Compound	H-2 ($J_{2,3}$)	H-3 ($J_{2,3'}$)	H-3' ($J_{3,3'}$)	H-4 ($J_{3,4}$)	H-5 ($J_{3',4}$)	H-6 ($J_{4,5}$)	H-6' ($J_{5,6}$)	NH ($J_{5,6'}$)	($J_{6,6'}$)
7	4.65 (8.7)	2.90 (10.7)	~2 (12.5)	4.60 (5.7)	5.26 (10.8)	4.45 (6.6)	4.20 (3.5)	6.45 (5.4)	(12.3)
8	4.98-4.85 (8.7)	3.12 (~11)	2.35 (12.7)	4.98-4.85 (5.7)	5.69 (~10)	4.83 (~6)	4.63 (3.6)	6.92 (5.5)	(12.3)
9	4.90 (7.0)	2.52 (13.0)	[a] (14.5)	5.10 (2.8)	4.64 (7.6)	←4.41-4.24→ (7.6)	(3.3)	6.52 (5.2)	(12.5)
10	5.22 (7.0)	2.93 (12.6)	2.37 (14.6)	5.53 (2.8)	5.03 (7.4)	4.77 (7.7)	4.65 (3.4)	7.03 (5.4)	(12.4)
12	4.99 (10.7)	2.89 (9.2)	[a] (13.8)	3.96 (7.7)	4.52 (9.4)	4.42 (9.6)	3.85 (5.1)	6.28 (10.2)	(9.8)
13	5.47 (9.2)	2.89 (11.4)	2.79 12.0	5.05 (6.0)	4.48 (9.7)	4.11 (4.0)	4.03 (5.6)	9.53 (5.8)	(12.3)
14	4.69 (9.0)	←3.25-2.97→ (10.8)		5.13 (6.0)	4.47 (9.6)	4.09 (3.8)	4.10 (5.8)	(~6.0)	(11.2)
1[b]	4.06 (6.9)	←2.32-2.06 → (4.1)		←	3.92–3.63		→		

For compounds **7-10**, **13-14** H-3 refers to the H *trans*, H-3' to the H *cis* with respect to the NHR group at C-2. [a]Overlapped with CH_3CO. [b]Ammonium salt.

9 and **10** indicated that they posses an *arabino* configuration, as their coupling constants were very similar[11] to those of the analogous 2,4,6-tri-*O*-benzoyl-D-*arabino*-hexono-1,5-lactone. Furthermore, *O*- and *N*-debenzoylation of **10** (5N aqueous HCl, reflux, 20h) followed by acetylation, afforded the previously synthesized lactone **7**. The diastereoselectivity may be explained if the enonolactones **5** and **6** are hydrogenated in their preferred ^5H_O conformation.[8,11a,12] In this form, the acyloxymethyl group al C-5 is *quasi*-axially oriented, preventing the addition of hydrogen from the α-face. Compounds **7-10** are acylated derivatives of the (2S,4S,5R)-4,5,6-trihydroxynorleucine in the 1,4- and 1,5-lactone forms.

Alternatively, a 3-deoxylactone precursor (**12**) of the trihydroxynorleucine **1** was prepared from **2** in a higher yield (67%), compared to that obtained for the synthesis of **7-10**, *via* the unsaturated lactones **3-6**. Hydrogenation of the previously described[8] compound **11** afforded diastereoselectively the 3-deoxylactone **12** (94% yield), mp 235-237 °C, $[\alpha]_D$ +108° (*c* 1, DMSO). The configuration for the C-2 of **12** was established by means of chemical transformations. Thus, hydrolysis of the benzylidene group of **12** (0.25% conc. HCl in acetone, reflux, 1.5 h) afforded **13** (95.5% yield), mp 160-161 °C, $[\alpha]_D$ -10° (*c* 1, H_2O). Conventional acetylation of **13** led to a product (90% yield), which showed the same physical and spectroscopic properties as **7**, previously obtained from **3**. The reason for the high diastereoselectivity in the hydrogenation of **11** is not obvious. However, it seems that the vinylic acetamide group is involved, as for the 2-acetoxy analogous of **11** no selective hydrogenation, under the same conditions, was observed.

Table 2. ^{13}C-NMR Data for Compounds **7-10** and **12-14**.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
7	173.9[a]	49.7	32.0	75.1	70.9	61.7
8	174.1	50.3	32.8	75.6	71.8	62.5
9	170.9[a]	45.7	32.0	65.1	76.6	62.4
10	170.8	46.3	32.2	66.2	77.2	63.2
12[b]	169.8[a]	44.6	29.9	68.0	72.5	67.1
13	175.0[a]	51.0	29.8	79.3	72.5	62.7
14	174.1	50.3	28.4	79.9	71.6	62.5
1[c]	175.2	53.6	32.9	75.3[d]	69.9[d]	63.1

[a]Assignments may be interchanged with CH_3CO. [b]PhCH δ 100,0. [c]Ammonium salt. [d]Assignment may be reversed.

Hydrolysis of **12** (5N aqueous HCl, reflux, 1.5 h) led to the 1,4-lactonic form of (2S,4S,5R)-4,5,6-trihydroxynorleucine as the crystalline hydrochloride (**14**, 85% yield, overall yield from **2** 57%), mp 185 °C, $[\alpha]_D$ -10° (*c* 0.8, H_2O). Compound **14** was applied to a Dowex 50 W (H^+) column, and eluted with 1M aq. ammonia. On evaporation, the ammonium salt of **1** [mp 173-174 °C, $[\alpha]_D$ -17.8° (*c* 0.6, H_2O)] was obtained.

References and Notes.

1. Wagner, I.; Musso, H. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 816-828.
2. a) Drauz, K.; Kleeman, A.; Martens, J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 584-608,
   b) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*. Pergamon Press: Oxford, 1989;
   c) Corey, E. J.; Lee, D.-H.; Choi, S. *Tetrahedron Lett.* **1992**, *33*, 6735-6738, and references therein.
3. Cintas, P. *Tetrahedron* **1991**, *47*, 6079-6111.
4. a) Lederkremer, R. M.; Varela, O. *Advan. Carbohydr. Chem. Biochem.* **1994**, *50*, 125-209;
   b) Bruce, I.; Fleet, G. W. J.; di Bello, I. C.; Winchester, B. *Tetrahedron* **1992**, *48*, 10191-10200 and references therein.
5. Vekemans, J. A. J. M.; de Bruyn, R. G. M.; Caris, R. C. H. M.; Kokx, A. J. P. M.; Konings, J. J. H. G.; Godefroi, E. F.; Chittenden, G. J. F. *J. Org. Chem.* **1987**, *52*, 1093-1099.
6. Nin, A. P.; Varela, O.; Lederkremer, R. M. *Tetrahedron* **1993**, *49*, 9459-9464.
7. Wolfrom, M. L.; Cron, M. J. *J. Am. Chem. Soc.* **1952**, *74*, 1715-1716.
8. Horton, D.; Thomson, J. K; Varela, O.; Nin, A. P.; Lederkremer, R. M. *Carbohydr. Res.* **1989**, *193*, 49-60.
9. a) Marino, M. C.; Varela, O.; Lederkremer, R. M. *Carbohydr. Res.* **1991**, *220*, 145-153; b) Moradei, O.; du Mortier, C.; Varela, O.; Lederkremer, R. M. *J. Carbohydr. Chem.* **1991**, *10*, 469-479;
   c) Jeroncic, L. O.; Fernández Cirelli, A.; Lederkremer, R. M. *Carbohydr. Res.* **1987**, *167*, 175-186. d) Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc. Perkin Trans. I* **1975**, 1480-1492.
10. All new compounds gave satisfactory elemental analysis. Optical rotations were measured for 1% solutions in $CHCl_3$, unless otherwise indicated.
11. a) Lederkremer, R. M.; Litter, M. I.; Sala, L. F. *Carbohydr. Res.* **1974**, *36*, 185-187; b) Nelson, C. R. *Carbohydr. Res.* **1987**, *163*, 275-278.
12. Varela, O.; Fernández Cirelli, A.; Lederkremer, R. M. *Carbohydr. Res.* **1979**, *70*, 27-35.

(*Received in USA* 12 *August* 1994; *revised* 17 *October* 1994; *accepted* 18 *October* 1994)