Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 6, pp. 1811-1818, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00216-9

Synthesis of Carbohydrate-Based Monomers that are Precursors for the Preparation of Stereoregular Polyamides

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Abstract: The syntheses of some derivatives of 5-amino-5-deoxy-L-arabinonic acid, 5-amino-5-deoxy-D-xylonic acid and (*S*)-5-amino-4-hydroxypentanoic acid have been performed in several steps from L-arabinose, D-xylose and (S)-(+)-glutamic acid, respectively. These ω-aminoacids are precursors of bifunctional monomers that could be used for the preparation of optically active polyamides.

INTRODUCTION

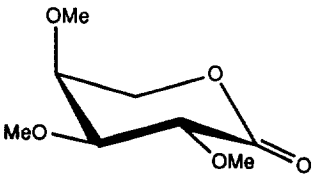
Amongst the different natural sources that are easily available, carbohydrates stand out as highly convenient for the preparation of novel stereoregular polymers[1-3], especially those with biodegradable properties. However, there are several limitations to their straighforward use, for instance, their multifunctionality, which must be reduced by making use of suitable protecting groups in order to avoid side reactions. Our efforts are currently being addressed to explore the possibilities of the preparation of stereoregular polyamides resulting from the condensation of ω-aminoacids derived from sugars by applying the active ester polycondensation method. In this sense, some derivatives of 6-amino-6-deoxy-D-gluconic acid[4], and a number of optically active carbohydrate-based polymers have already been described[5,6].

In this paper, we report on the preparation of some derivatives of 5-amino-5-deoxy-L-arabinonic acid, 5-amino-5-deoxy-D-xylonic acid and (*S*)-5-amino-4-hydroxypentanoic acid which are precursors of bifunctional monomers for linear polycondensations.

RESULTS AND DISCUSSION

The synthesis of 5-amino-5-deoxy-2,3,4-tri-*O*-methyl-L-arabinonic acid **5** was carried out in 4 steps from 2,3,4-tri-*O*-methyl-L-arabino-1,5-lactone as previously described[7a]. Opening of the lactone ring in **1** by benzyl alcohol catalyzed by camphorsulfonic acid gave **2** in moderate yield. Subsequent reaction of the primary alcohol function with tosyl chloride afforded, after column chromatography, benzyl 5-*O*-tosyl-2,3,4-tri-*O*-methyl-L-arabinonate **3**. Nucleophilic substitution of the tosyl group of **3** with azide yielded **4** that was isolated as a syrup. Hydrogenation of this compound in the presence of hydrochloric acid gave the hydrochloride derivative **5**, that was obtained as a foam in quantitative yield.

Treatment of **5** with di-*tert*-butyl dicarbonate afforded the *N*-*tert*-butoxycarbonyl derivative **6** which



1

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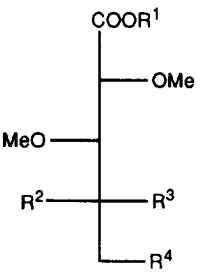
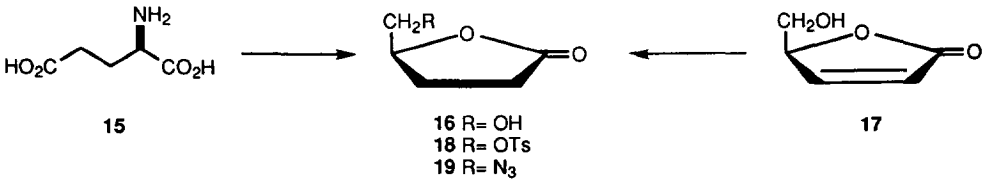


2 R^1= Bn, R^2= OMe, R^3= H, R^4= OH
3 R^1= Bn, R^2= OMe, R^3= H, R^4= OTs
4 R^1= Bn, R^2= OMe, R^3= H, R^4= N_3
5 R^1= H, R^2= OMe, R^3= H, R^4= NH_2HCl
6 R^1= H, R^2= OMe, R^3= H, R^4= NHBoc
7 R^1=Pcp, R^2= OMe, R^3= H, R^4= NHBoc
9 R^1= Bn, R^2= H , R^3= OMe, R^4= OH
10 R^1= Bn, R^2= H, R^3= OMe, R^4= OTs
11 R^1= Bn, R^2= H, R^3= OMe, R^4= N_3
12 R^1= H, R^2= H, R^3= OMe, R^4= NH_2HCl
13 R^1= H, R^2=H, R^3= OMe, R^4= NHBoc
14 R^1=Pcp, R^2= H, R^3= OMe, R^4= NHBoc

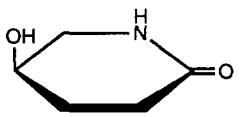
was isolated by column chromatography as an oil, and characterized as the active ester **7**.

The 5-amino-5-deoxy-2,3,4-tri-*O*-methyl-D-xylonic acid **12** and its derivatives were prepared following a similar sequence of reactions: opening of the lactone ring of **8**[7b], tosylation, nucleophilic substitution by azide, and finally hydrogenation in the presence of hydrochloric acid to obtain the aminoacid **12** (24%, overall yield). As in the case of **5**, the bifunctional monomer **14** was also obtained (47% yield; two steps from **12**).

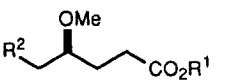
(*S*)-Dihydro-5-hydroxymethyl-2(3*H*)-furanone **16** was the key intermediate for the synthesis of the hydroxy amino acid derivative **22**, precursor of a chiral nylon-5 analogue having a single stereocenter by repeat unit. Compound **16** was readily prepared[8] by nitrous acid deamination, followed by borane reduction of commercially available and unexpensive (*S*)-(+)-glutamic acid **15**. Alternatively, **16** was synthesized by hydrogenation of butenolide **17**, which was obtained in good yield from D-ribonolactone by the Godefroi's procedure[9]. In both cases, **16** was isolated and purified as the crystalline tosylate **18**. Nucleophilic substitution of the tosyl group of **18** with sodium azide in DMF at 60 °C, led to the 5-azido lactone **19**. The specific rotation measured for **19** (+93) was higher than the value previously reported[10] for the product (+56) prepared from manitol, but it was coincident with that described by Olsen and co-workers[11]. Treatment of **19** with pulverized KOH in THF, in the presence of methyl iodide afforded, upon acidification, two main compounds. The product having smaller R_f was the desired acid derivative **20**, whereas the faster migrating one was spectroscopically identified as the methyl ester **21**. However, complete conversion of **19** into **20** was achieved in a single step[4] by hydrolysis of **21** upon addition of water to the reaction mixture, when the starting **19** had been consumed. The opening of the lactone ring was evidenced by the strong upfiel shift (1.15 ppm) of the H-4 signal in the ^{1}H-NMR spectrum of **20** with respect to the same resonance in that of **19**.



15 **16** R= OH; **18** R= OTs; **19** R= N_3 **17**



23



20 R^1= H, R^2= N_3
21 R^1= Me, R^2= N_3
22 R^1= H, R^2= NH_2HCl
24 R^1= H, R^2= NHBoc
25 R^1= Pcp, R^2= NHBoc

Catalytic hydrogenation of the azide function of **20** in the presence of hydrochloric acid, afforded the hydrochloride derivative **22**. In order to rule out any lactamization of **22**, we compared the spectral properties of this compound with those of the lactam **23**. Although **23** had already been synthesized,[10,11] no spectral data were reported. Therefore, we have prepared a sample of such a lactam by hydrogenation of **19** under neutral conditions. In the ^{13}C-NMR spectra the acid carbonyl signal of **22** appeared at lower field (8.3 ppm) than the lactam carbonyl resonance of **23**. The signal of C-5 (bonded to N) was also affected, being shifted downfield in **23** with respect to **22**, due to the cyclyzation.

Protection of the amino function of **22** with di-*tert*-butyl dicarbonate led to the syrupy *N*-Boc derivative **24** which was isolated essentially pure from the reaction mixture. Compound **24** was characterized as the crystalline pentachlorophenyl ester **25**. Its ^{13}C-NMR spectrum was very similar to that of the acid precursor **24**, except for the upfield displacement of C-1 due to the esterification. The bifunctional derivatives of ω-aminoacids, **7**, **14**, and **25** have the carbonyl function activated, and might be thought therefore suitable for polymerization after removal of the *N*-protecting group. However, it is known[5] that in that case an intramolecular reaction takes place leading to the corresponding six membered cyclic lactam.

EXPERIMENTAL

General.- Chemicals were all used as purchased from Aldrich Chemical Co. Solvents were dried and purified when necessary, by appropriate standard procedures. Optical rotations were measured at 20 ± 5 °C with a Bellingham & Standley Inc., P20 polarimeter (5-cm cell). TLC was performed on silica gel 60 F_{254} (Merck) with detection by UV light, phosphomolybdic acid (7% w/v) in 95% ethanol or with anisaldehyde (5% v/v) in 95% ethanol containing 5% sulfuric acid. Flash column chromatography: Merck silica gel 60 (230-400 mesh). FT IR spectra (films or KBr discs) were recorded with a Michelson 100 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker 200 AC-P or a Bruker AMX-500 spectrometers. Chemical shifts are reported as parts per million downfield from tetramethylsilane. The following abbreviations are used to present the ^{1}H-NMR spectra results: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Elemental analyses were determined in the Microanalysis Laboratories at the Universidad de Sevilla and the Universidad Complutense de Madrid. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Mass spectra were obtained using a Kratos MS80RFA

instrument. Compounds characterized by exact mass were shown to be pure by TLC and NMR spectroscopy.

***Benzyl 2,3,4-tri-O-methyl-L-arabinonate* (2).-** To a solution of 2,3,4-tri-*O*-methyl-L-arabino-1,5-lactone[7a] **1** (12.0 g, 63.15 mmol) in benzyl alcohol (13.2 mL, 127.5 mmol) was added a catalytic amount of camphorsulfonic acid. After heating for 3 days at 50 °C, the solution was diluted with dichloromethane (50 mL) and washed with an aqueous solution of sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3 x 40 mL) and the combined organic extracts were concentrated under diminished pressure.The residue was chromatographed on silica gel column (eluent 2:1 hexane/ethyl acetate) to give **5** as an oil (9.5 g, 51%); $[\alpha]_D$ + 37 (*c* 1, chloroform); υ_{max} 3479 (OH), 1745 (CO) cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 3.27, 3.38, 3.48 (s, 9H, 3 OMe), 3.36 (ddd, 1H, $J_{3,4}$ 8.7 Hz, H-4), 3.64 (dd, 1H, $J_{4,5}$ 2.6 Hz, $J_{5,5'}$ 12.1 Hz, H-5), 3.74 (dd, 1H, H-3), 3.90 (dd, 1H, $J_{4,5'}$ 3.3 Hz, H-5'), 4.00 (d, 1H, $J_{2,3}$ 2.5 Hz, H-2), 5.24 (d, 1H, *J* 12.1 Hz, CH_2Ph), 5.25 (d, 1H, *J* 12.1 Hz, CH_2Ph), 7.39 (m, 5H, Ph); ^{13}C, δ 57.4, 58.7, 60.0 (3 OCH_3), 58.9 (C-5), 66.5 (CH_2Ph), 79.3, 79.7, 80.1 (C-2/4), 128.2, 128.3, 128.5 (CH_2**Ph**), 171.1 (C-1). Mass spectrum: *m/z* 298.1437 (calcd for $C_{15}H_{22}O_6$: 298.1416).

***Benzyl 2,3,4-tri -O-methyl- 5-O-tosyl-L-arabinonate* (3).-** To a cooled solution of benzyl 2,3,4-tri-O-methyl-L-arabinonate **2** (6.0 g, 20.1 mmol) in dichloromethane (22.0 mL) containing dry pyridine (3.2 mL, 40.26 mmol) was added tosyl chloride (5.7 g, 30.19 mmol) in small portions. When the addition was completed, the solution was allowed to warm to room temperature and then stirred for 24 h. The solvents were evaporated under diminished pressure, and the residue was chromatographed on silica gel column (eluent 2:1 hexane/ethyl acetate) to give **3** as an oil (7.5 g, 83%); $[\alpha]_D$ + 13.3 (*c* 1, chloroform); υ_{max} 1744 (CO) cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 2.43 (s, 3H, CH_3), 3.12, 3.26, 3.44 (s, 9H, 3 OMe), 3.52 (ddd, 1H, $J_{3,4}$ 8.6 Hz, H-4), 3.68 (dd, 1H, H-3), 4.00 (d, 1H, $J_{2,3}$ 2.3 Hz, H-2), 4.10 (dd, 1H, $J_{4,5}$ 2.2 Hz, $J_{5,5'}$ 10.8 Hz, H-5), 4.34 (dd, 1H, $J_{4,5'}$ 3.8 Hz, H-5'), 5.23 (d, 1H, *J* 12.1 Hz, CH_2Ph), 5.22 (d, 1H, *J* 12.1 Hz, CH_2Ph), 7.36, 7.78 (2m, 9H, Ph); ^{13}C, δ 21.5 (CH_3), 58.3, 58.5, 59.9 (3 OCH_3), 66.6 (CH_2Ph), 67.4 (C-5), 77.3, 79.1, 80.0 (C-2/4), 127.8, 128.3, 128.4, 129.7, 132.6, 135.0, 144.7 (Ph), 170.7 (C-1). Anal. calcd. for $C_{22}H_{28}O_8S$: C, 58.39; H, 6.23; S, 7.08. Found: C, 58.31; H, 6.31; S, 7.06.

***Benzyl 5-azido-5-deoxy-2,3,4-tri -O-methyl-L-arabinonate* (4).-** To a solution of **3** (1.9 g, 4.19 mmol) in dry dimethylformamide (20.0 mL) was added NaN_3 (0.44 g, 6.76 mmol), and then stirred for 2 h at 100 °C. The solution was poured into acetone (1 L), and the solid separated was filtered out and washed with acetone. The filtrate and washings were combined, concentrated, and the residue chromatographed on silica gel column (eluent 2:1 hexane/ethyl acetate) to give **4** as an oil (1.1 g, 82.0%); υ_{max} 2102 (N_3), 1748 (CO) cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 3.22, 3.42, 3.48 (s, 9H, 3 OMe), 3.28 (dd, 1H, $J_{4,5}$ 2.8 Hz, $J_{5,5'}$ 13.2 Hz, H-5), 3.47 (ddd, 1H, $J_{3,4}$ 8.7 Hz H-4), 3.67 (dd, 1H, $J_{4,5'}$ 4.0 Hz, H-5'), 3.68 (dd, 1H, H-3), 4.06 (d, 1H, $J_{2,3}$ 2.4 Hz, H-2), 5.24 (d, 1H, *J* 12.1 Hz, CH_2Ph), 5.26 (d, 1H, *J* 12.1 Hz, CH_2Ph), 7.35 (m, 5H, Ph); ^{13}C, δ 58.6, 58.6, 60.0 (3 OCH_3), 50.8 (C-5), 66.6 (CH_2Ph), 79.4, 80.3, 80.7 (C-2/4), 128.3, 128.4, 135.1 (Ph), 170.1 (C-1). Anal. calcd. for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.54; N,12.99. Found: C, 55.83; H, 6.53; N, 12.71.

***5-Amino-5-deoxy-2,3,4-tri-O-methyl-L-arabinonic acid hydrochloride* (5).-** A solution of **4** (0.85 g, 2.63 mmol) in 2M HCl (4.6 mL) was hydrogenated (40 psi) at room temperature in the presence of 10% Pd-C (0.09 g). After 4 h, the mixture was filtered, the insoluble material washed with water, and the

combined filtrate and washings evaporated to give **5** as a foam, in quantitative yield. This compound was used without further purification; $[\alpha]_D$ -28 (*c* 1, water); υ_{max} 3426 (NH_2, OH), 1611 (CO) cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 2.92 (dd, 1H, $J_{4,5}$ 7.6 Hz, $J_{5,5'}$ 12.5 Hz, H-5), 3.13 (dd, 1H, $J_{4,5'}$ 3.7 Hz, H-5'), 3.19, 3.20, 3.24 (s, 9H, 3 OMe), 3.45 (ddd, 1H, $J_{3,4}$ 5.2 Hz, H-4), 3.72 (dd, 1H, H-3), 3.84 (d, 1H, $J_{2,3}$ 2.3 Hz, H-2); ^{13}C, δ 60.1, 60.7, 62.3 (3 OCH_3), 41.6 (C-5), 79.7 (C-4), 81.1 (C-3), 82.7 (C-2), 177.0 (C-1).

***Pentachlorophenyl 5-(tert-butoxycarbonylamino)-5-deoxy-2,3,4-tri-O-methyl-L-arabinonate*(7).-** To a stirred solution of **5** (0.6 g, 2.46 mmol) in acetonitrile (20 mL), di-*tert*-butyl dicarbonate (0.53 g, 2.43 mmol) and triethylamine (0.3 mL, 2.20 mmol) were added. The mixture was stirred for 24 h at room temperature, then concentrated under diminished pressure, and the residue was treated with a mixture of water and dichloromethane. The organic phase was washed with water (3.0 mL), dried ($MgSO_4$), and concentrated to give **6** as a syrup that was redissolved in dry ethyl acetate (10 mL). To this solution, pentachlorophenol (0.69 g, 2.64 mmol) and dicyclohexylcarbodiimide (0.54 g, 2.64 mmol) were added. After 24 h of stirring, at room temperature, the solid formed was separated and washed with ethyl acetate. The filtrate and washings were combined, concentrated and chromatographed on silica gel column (eluent 1:1 hexane/ether) to give **7** (0.7 g, 51%) as a syrup; $[\alpha]_D$ +4 (*c* 1 chloroform) υ_{max} 3470, 3340 (NH), 1789, 1713, 1507 (CO) cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 1.47 (s, 9H, 3 CH_3), 3.45, 3.50, 3.64 (s, 9H, 3 OMe), 3.50 (m, 3H, H-4/5'), 3.85 (dd, 1H, $J_{3,4}$ 7.3 Hz, H-3), 4.40 (d, 1H, $J_{2,3}$ 2.1 Hz, H-2), 4.86 (bs, 1H, NH); ^{13}C, δ 28.3 (CCH_3), 57.5, 59.8, 60.7 (3 OCH_3), 38.4 (C-5), 78.2 (C-4), 79.8 (C-3), 80.5 (C-2), 79.4 (CCH_3), 127.4, 131.8, 132.2, 143.9, 149.8 (Ph), 155.8 (CONH), 168.1 (C-1). Anal. calcd. for $C_{19}H_{24}Cl_5NO_7$: C, 41.06; H, 4.35; N, 2.52. Found: C, 41.22; H, 4.35; N, 2.19.

***Benzyl 2,3,4-tri-O-methyl-D-xylonate* 9 .-** It was obtained from 2,3,4-tri-*O*-methyl-D-xylo-1,5-lactone[7b] **8** as a syrup (41% yield) following the procedure decribed above for **2**; $[\alpha]_D$ +40 (*c* 1, chloroform), υ_{max} 3460 (OH), 1745 (CO) cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 3.33, 3.34, 3.42 (s, 9H, 3 OMe), 3.50 (ddd, 1H, $J_{3,4}$ 6.3 Hz, H-4), 3.59 (dd, 1H, $J_{4,5}$ 4.8 Hz, $J_{5,5'}$ 12.0 Hz, H-5), 3.76 (dd, 1H, H-3), 3.80 (dd, 1H, $J_{4,5'}$ 3.9 Hz, H-5'), 4.00 (d, 1H, $J_{2,3}$ 3.3 Hz, H-2), 5.21 (d, 1H, *J* 12.1 Hz, CH_2Ph), 5.26 (d, 1H, *J* 12.1 Hz, CH_2Ph), 7.36 (m, 5H, Ph); ^{13}C, δ 58.3, 58.5, 59.9 (3 OCH_3), 60.6 (C-5), 66.4 (CH_2Ph), 79.6, 81.2, 81.3 (C-2/4), 128.1, 128.3 (CH_2**Ph**), 170.2 (C-1). Anal. calcd. for $C_{15}H_{22}O_6$: C, 60.38; H, 7.43. Found: C, 60.13; H, 7.65.

***Benzyl 2,3,4-tri-O-methyl-5-O-tosyl-D-xylonate* 10 .-** It was obtained from **9** as a syrup (70% yield) by the procedure decribed above for **3**; $[\alpha]_D$ +40 (*c* 0.5, chloroform); υ_{max} 1748 (CO) cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 2.43 (s, 3H, CH_3), 3.23, 3.35, 3.38 (s, 9H, 3 OMe), 3.68 (m, 1H, H-4), 3.93 (d, 1H, $J_{2,3}$ 2.5 Hz, H-2), 4.07 (m, 2H, $J_{4,5}$ 2.2 Hz, H-3,5), 4.29 (dd, 1H, $J_{4,5'}$ 6.3 Hz, $J_{5,5'}$ 11.1 Hz, H-5'), 5.17 (d, 1H, *J* 12.1 Hz, CH_2Ph), 5.25 (d, 1H, *J* 12.1Hz, CH_2Ph), 7.33 (m, 5H, Ph), 7.78 (m, 5H, Ph); ^{13}C, δ 21.5 (CH_3), 58.3, 58.5, 59.7 (3 OCH_3), 66.8 (CH_2Ph), 70.2 (C-5), 78.4, 79.0, 80.3 (C-2/4), 127.9, 128.4, 128.5, 129.8, 132.7, 135.3, 144.7 (Ph), 170.3 (C-1). Anal. calcd. for $C_{22}H_{28}O_8S$: C, 58.39; H, 6.23. Found: C, 58.32; H, 5.99.

***Benzyl 5-azido-5-deoxy-2,3,4-tri-O-methyl-D-xylonate* 11 .-** It was obtained from **10** as a syrup (84% yield) by the procedure decribed above for **4**; $[\alpha]_D$ +38 (*c* 1, chloroform); υ_{max} 2100 (N_3), 1747 (CO) cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 3.34, 3.41, 3.45 (s, 9H, 3 OMe), 3.32 (dd, 1H, $J_{4,5}$ 3.3 Hz, $J_{5,5'}$ 13.1 Hz, H-5), 3.45 (dd, 1H, $J_{4,5'}$ 6.8 Hz, H-5'), 3.55 (ddd, 1H, $J_{3,4}$ 5.9 Hz, H-4), 3.70 (dd, 1H, H-3), 3.95 (d, 1H,

$J_{2,3}$ 3.5 Hz, H-2), 5.20 (d, 1H, *J* 12.1 Hz, CH_2Ph), 5.25 (d, 1H, *J* 12.1 Hz, CH_2Ph), 7.36 (m, 5H, Ph); ^{13}C, δ 57.8, 59.0, 60.1 (3 OCH_3), 49.5 (C-5), 66.7 (CH_2Ph), 78.9 (C-4), 79.4 (C-3), 80.7 (C-2), 128.5, 128.6, 135.2 (Ph), 170.9 (C-1). Anal. calcd. for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.54; N, 12.99. Found: C, 56.08; H, 6.93; N, 13.11.

***5-Amino-5-deoxy-2,3,4-tri-O-methyl-D-xylonic acid hydrochloride* 12** .- It was obtained from **11** as a foam, in quantitative yield, following the procedure decribed above for **5**. It was used in the next reaction without further purification; $[\alpha]_D$ -44 (*c* 0.5 water); υ_{max} 3400 (NH_2, OH), 1731, 1620 (CO) cm^{-1}. NMR data (D_2O): ^1H, δ 2.96 (dd, 1H, $J_{4,5}$ 8.0 Hz, $J_{5,5'}$ 13.0 Hz, H-5), 3.15 (dd, 1H, $J_{4,5'}$ 3.6 Hz, H-5'), 3.27, 3.31, 3.33 (s, 9H, 3 OMe), 3.68 (ddd, 1H, $J_{3,4}$ 5.2 Hz, H-4), 3.81 (dd, 1H, H-3), 3.97 (d, 1H, $J_{2,3}$ 2.8 Hz, H-2); ^{13}C, δ 59.0, 59.2, 60.0 (3 OCH_3), 40.2 (C-5), 76.7 (C-4), 78.1 (C-3), 81.1 (C-2), 175.1 (C-1).

***Pentachlorophenyl* 5-(tert-*butoxycarbonylamino*)-5-deoxy-2,3,4-*tri*-O-*methyl*-D-*xylonate* (14)**.- It was obtained as a syrup (47% yield) by the procedure decribed above for **7**; $[\alpha]_D$ +10 (*c* 1 chloroform); υ_{max} 3440, 3384 (NH), 1788, 1708, 1512 (CO) cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 1.45 (s, 9H, 3 CH_3), 3.50, 3.57, 3.63 (s, 9H, 3 OMe), 3.60 (m, 3H, H-4/5'), 3.93 (dd, 1H, $J_{3,4}$ 6.2 Hz, H-3), 4.48 (d, 1H, $J_{2,3}$ 2.8 Hz, H-2), 5.00 (bt, 1H, NH); ^{13}C, δ 28.4 (CCH_3), 58.5, 59.5, 60.5 (3 OCH_3), 40.0 (C-5), 79.4 (C-4), 80.1 (C-3), 81.3 (C-2), 79.4 (CCH_3), 127.3, 132.2 (Ph), 156.5 (CONH), 167.3 (C-1). Anal. calcd. for $C_{19}H_{24}Cl_5NO_7$: C, 41.06; H, 4.35; N, 2.52. Found: C, 40.91; H, 4.46; N, 2.27. Mass spectrum: *m/z* 552.9960 (calcd. for $C_{19}H_{24}Cl_5NO_7$: 552.9995).

***(S)-Dihydro-5-tosyloxymethyl-2(3H)-furanone* 18** .- It was prepared from *(S)*-(+)-glutamic acid **15** as previously described[8]. Alternatively, **18** can be synthesized from D-ribono-1,4-lactone[9] *via* hydrogenation and tosylation of butenolide **17**.

***(S)-Dihydro-5-azidomethyl-2(3H)-furanone* 19** .- To a solution of **18** (1.0 g, 3.70 mmol) in dry DMF (30 mL), NaN_3 (0.71 g, 11 mmol) was added, and the mixture was stirred for 1 h at 60 °C. The solvent was evaporated under diminished pressure and the residue extracted with dichloromethane. The extract was filtered, dried ($MgSO_4$) and concentrated, to afford **19** (0,49 g, 94 %) essentialy pure. For analytical purposes a sample of **19** (0.10 g) was chromatographed on silica gel column (eluent 9:1 hexane/ethyl acetate) to give a colorless oil, $[\alpha]_D$ +93 (*c* 2, chloroform); NMR data ($CDCl_3$): ^1H, δ 1.95 (m, 1H, H-3'), 2.23 (m, 1H, H-3), 2.46 (m, 2H, H-2,2'), 3.35 (dd, 1H, $J_{4,5}$ 5.0 Hz, $J_{5,5'}$ 13.3 Hz, H-5), 3.50 (dd, 1H, H-5'), 4.55 (m, 1H, $J_{3,4} = J_{3',4}$ 7 Hz, $J_{4,5}$ 3.7 Hz, H-4); ^{13}C, δ 24.5 (C-3), 28.2 (C-2), 54.2 (C-5), 78.2 (C-4), 176.4 (C-1). Anal. calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00. Found: C, 42.39; H, 4.99.

***(S)-5-Azido-4-methoxypentanoic acid* 20** .- To a solution of crude **19** (0.50 g, 3.54 mmol) in dry THF (5 mL) freshly pulverised KOH (0.3 g, 5.3 mmol) and methyl iodide (0.5 mL) were added. The suspension was stirred in the dark for 16 h at room temperature, then poured into water, stirred for 1 h more and extracted with ethyl ether. The aqueous phase was acidified (pH 4) with concentrated HCl, and extracted several times with ethyl ether. The combined organic extracts were concentrated to a syrup which was chromatographed (eluent 4:1 hexane/ethyl acetate) to give **21** (0.52 g, 85 %) as a colorless oil, $[\alpha]_D$ -17 (*c* 1, chloroform); NMR data ($CDCl_3$): ^1H, δ 1.87 (q, 2H, *J* 7.2 Hz, H-3,3'), 2.47 (t, 2H, *J* 7.2 Hz, H-2,2'), 3.31 (m, 2H, H-5,5'), 3.40 (m, 1H, H-4), 3.43 (s, 3H, OCH_3); ^{13}C, δ 27.0 (C-3), 29.7 (C-2), 53.2 (C-5), 57.8 (OCH_3), 79.1 (C-4), 179.1 (C-1). Anal. calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40. Found:

C, 42.13; H, 6.73.

(S)-*5-Amino-4-methoxypentanoic acid hydrochloride* 22 .- A solution of **20** (0.52 g, 3 mmol) in 2M HCl (4 mL) was hydrogenated (45 psi) at room temperature in the presence of 10% Pd-C (10 mg). After 16 h, the reaction mixture was filtered and the filtrate concentrated under diminished pressure. The residue crystallized from methanol-ethyl ether to give **22** (0.48 g, 87 %), mp 126-128 °C, $[\alpha]_D$ +21 (*c* 1, H_2O); NMR data (D_2O): ^1H, δ 1.86 (q, 2H, *J* 7.3 Hz, H-3,3'), 2.44 (t, 2H, *J* 7.3 Hz, H-2,2'), 2.95 (dd, 1H, $J_{4,5}$ 8.3 Hz, H-5), 3.18 (dd, 1H, $J_{5,5'}$ 13.4 Hz, H-5'), 3.37 (s, 3H, OCH_3), 3.59 (m, 1H, $J_{4,5'}$ 3.2 Hz, H-4); ^{13}C, δ 26.5 (C-3), 30.0 (C-2), 42.5 (C-5), 57.7 (OCH_3), 77.2 (C-4), 178.5 (C-1). Anal. calcd for $C_6H_{13}NO_3.1.1$ HCl: C, 38.48; H 7.59; N,7.48. Found: C, 38.26; H,7.28; N, 7.42.

(S)-*5-Hydroxy-2-piperidinone* 23 .- A solution of **19** (90 mg, 0.64 mmol) in methanol (5 mL) was hydrogenated (50 psi) at room temperature in the presence of 10% Pd-C (30 mg). After 8 h, the catalyst was filtered out and the solvent evaporated to give a residue that crystallized after standing overnight under vaccum. The crystals were washed with ethyl ether to give **23** (50 mg, 55%); mp 120-122 °C (Lit.[10] 124-125 °C); NMR data (DMSO-d_6): ^1H, δ 1.73 (m, 2H, H-3,3'), 2.18 (m, 2H, H-2.2'), 2.97 (dd, 1H, $J_{4,5}$ 5.1 Hz, $J_{5,5'}$ 12.4 Hz H-5), 3.22 (dd, $J_{4,5'}$ 3.8, H-5'), 3.85 (m, 1H, H-4), 4.23 (bs, 1H, OH), 7.25 (bs, 1H, NH); ^{13}C, δ 27.9 (C-3), 28.4 (C-2), 48.3 (C-5), 62.4 (C-4), 170.2 (C-1).

(S)-*5-(tert-Butoxycarbonylamino)-4-methoxypentanoic acid* 24 .- To a suspension of **22** (0.3 g, 1.65 mmol) in dry acetonitrile (15 mL), di-*tert*-butyl dicarbonate (0.396 g, 1.81 mmol) and triethylamine (0.26 mL, 1.81 mmol) were added. The mixture was stirred at room temperature for 24 h, concentrated and the resulting residue suspended in ethyl acetate. The solid formed was filtered out, and the filtrate was concentrated to afford **24** (0.35 g, 85 %) which was used in the next step without further purification; NMR data ($CDCl_3$): ^1H, δ 1.38 (s, 9H, (CCH_3), 1.79 (q, 2H, *J* 7.3 Hz, H-3,3'), 2.38 (t, 2H, *J* 7.3Hz, H-2,2'), 3.06-3.30 (m, 3H, H-4,5,5'), 3.35 (s, 3H, OCH_3), 4,95 (bs, 1H, NH), 9.18 (bs, 1H, CO_2H); ^{13}C, δ 26.5 (C-3), 28.3 (CCH_3), 29.7 (C-2), 42.5 (C-5), 57.1 (OCH_3), 78.8 (C-4), 79.4 (CCH_3), 156.2 (CONH), 177.8 (C-1).

***Pentachlorophenyl* (S)-*5-(tert-butoxycarbonylamino)-4-methoxypentanoate* (25).-** To a solution of crude **24** (0.35 g, 1.40 mmol) in dry ethyl acetate (7 mL), pentachlorophenol (0.4 g, 1.48 mmol) and dicyclohexylcarbodiimide (0.31 g, 1.48 mmol) were added. After stirring 24 h at room temperature, the suspension was filtered and the solid washed with ethyl acetate. The combined filtrate and washings were concentrated, and the residue purified by column chromatography (eluent 24:1 hexane/ethyl acetate). The solvent was evaporated from the fractions containing the product, affording crystalline **25** (0.59 g, 85 %), mp 116-118 °C (from ethanol), $[\alpha]_D$ -3.5 (*c* 1, chloroform); NMR data ($CDCl_3$): ^1H, δ 1.47 (s, 9H, (CCH_3), 1.99 (q, 2H, *J* 7.4 Hz, H-3,3'), 2.82 (t, 1H, *J* 7.4 Hz, H-2,2'), 3.28-3.35 (m, 2H, H-5,5'), 3.40 (m, 1H, H-4), 3.42 (s, 3H, OCH_3), 4.81 (bs, 1H, NH); ^{13}C, δ 26.4 (C-3), 28.4 (CCH_3), 29.3 (C-2), 42.2 (C-5), 57.3 (OCH_3), 78.4 (C-4), 79.5 (CCH_3), 127.6, 131.5, 132.0, 144.1 (Ph), 156.1 (CONH), 169.3 (C-1). Anal. calcd for $C_{17}H_{20}Cl_5NO_5$: C, 41.20; H, 4.07; N, 2.83. Found: C, 41.68; H, 4.10; N, 3.07.

ACKNOWLEDGMENTS

O. V. is indebted to DGICYT (Dirección General de Investigación Científica y Técnica de España) for granting a sabatical position (1/94 - 4/94) to work in a joint project with Dr. J. A. G. We thank the

CICYT (Comisión Interministerial de Ciencia y Tecnología de España; Grant MAT93-0555-C02) and Universidad de Buenos Aires (Project EX-173) for finantial support. O. V. is a Research Member of CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas de la República Argentina).

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(*Received in UK* 1 *April* 1996; *accepted* 8 *May* 1996)