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Stereoselective Synthesis of 4,5-Dihydroxy-D-*erythro*- and 4,5-Dihydroxy-D-*threo*-L-norvaline from D-Ribonolactone

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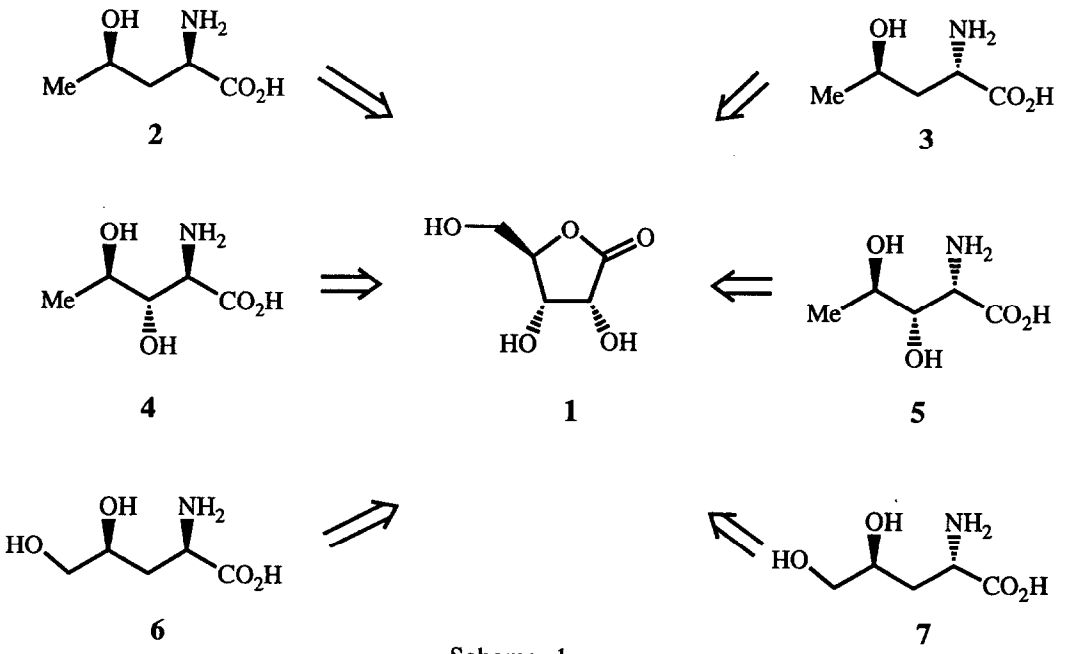
Abstract. Nitrogen functions have been introduced stereoselectively at the C-2 position in D-ribonolactone derivatives in order to prepare the title unnatural amino acids. The synthetic strategies lie in the inversion of configuration in S_N2-type substitution reactions and stereospecific hydrogenation of conveniently substituted butenolides. The threo-isomer is the key precursor in the synthesis of the antibiotic clavalanine.

INTRODUCTION

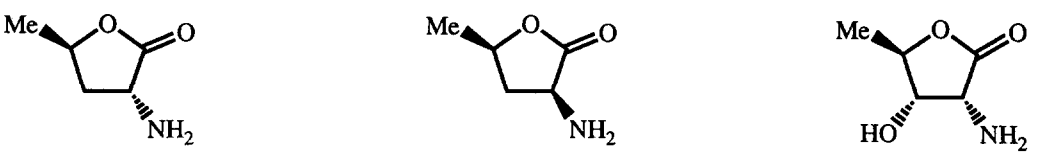
Non-protein hydroxy α-amino acids are widely extended among natural products isolated from very different sources.[1] Moreover, such kinds of compound, of natural or unnatural origin, have been used as precursors in the synthesis of β-lactams and aminopoliols.[2] All these facts have contributed to increase the interest of synthetic organic chemists in the last decade to find efficient and convenient methods in order to prepare these homochiral amino acids in a stereocontrolled manner.

D-Ribonolactone **1** has been shown to be a good chiral precursor to achieve the synthesis of several amino acids.[3,4] In particular, we have developed strategies to introduce stereoselectively an amino function at C-2 in several D-ribonolactone derivatives, allowing the obtention of lactones **2a-5a**, which are equivalent to the corresponding open-chain amino acids **2-5** (Scheme 1, Chart 1).[4] C-4 Position of D-ribonolactone is the stereogenic center that induces the configuration at C-2 in **2a-5a**.

In this paper we present the use of such a chiral precursor in the synthesis of two further amino acids, **6** and **7**. As far as we know, 4,5-dihydroxy-D-erythro-L-norvaline, **6**, was unknown previous to this work. The epimer, 4,5-dihydroxy-D-threo-L-norvaline, **7**, has been used as a key intermediate in the synthesis of the clavam antibiotic clavalanine (Ro 22-5417).[5]



Scheme 1



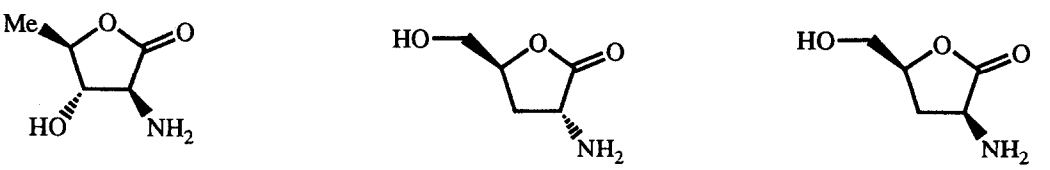


Chart 1

RESULTS AND DISCUSSION

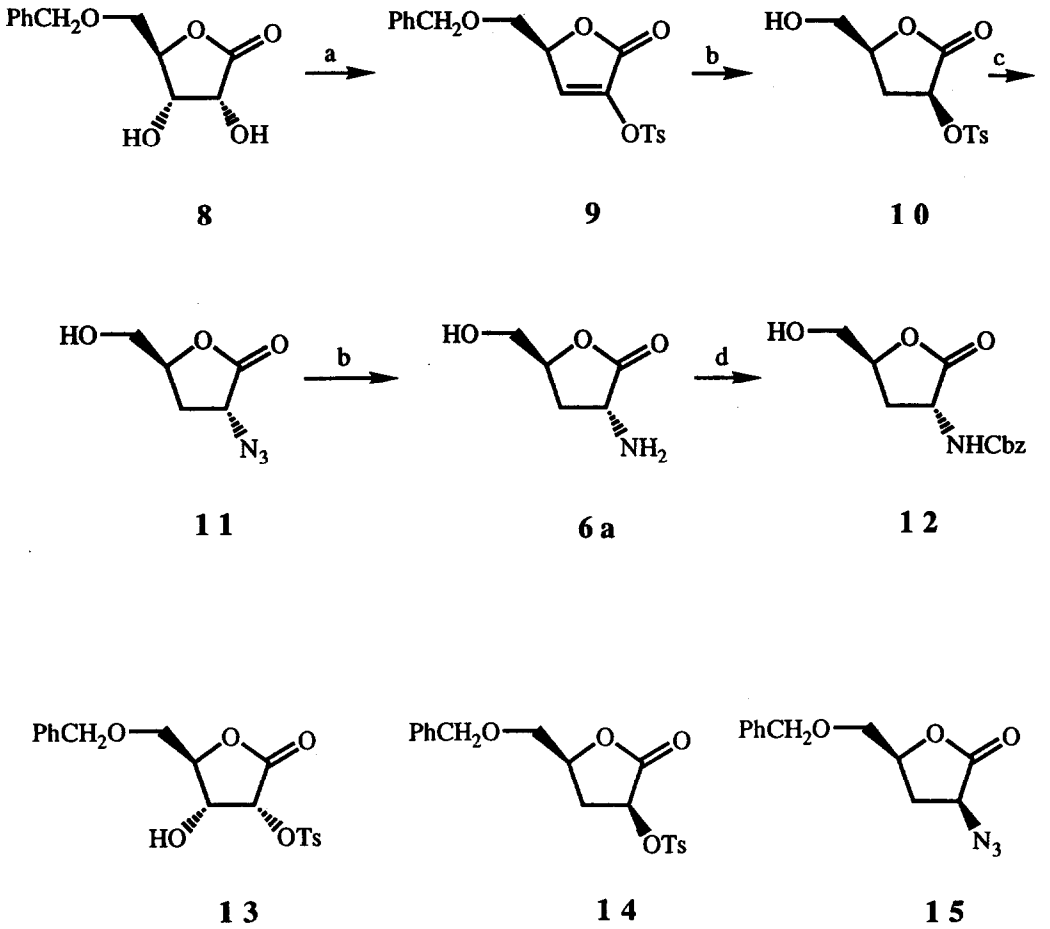
4,5-Dihydroxy-D-erythro-L-norvaline, 6.

Retrosynthetic analysis relates lactone **6a**, equivalent to amino acid **6**, with tosylate **10**. Nitrogen functionality may be introduced by reaction of **10** with sodium azide, with concomitant configurational inversion. In turn, tosylate **10** could be obtained by means of stereospecific hydrogenation of butenolide **9**.

The total synthesis of **6a** is depicted in Scheme 2 and was carried out as follows. 5-O-Benzyl-D-ribonolactone **8**[6] was converted into the unsaturated tosylate **9** (45% yield) by treatment with 2.5 mol of tosyl chloride in pyridine at room temperature for 24 h. In this reaction the hydroxy tosylate **13** was also produced in 17% yield. This compound was transformed into **9** almost quantitatively by reaction with acetic anhydride in pyridine at room temperature overnight. Butenolide **9** was submitted to hydrogenation under several conditions. Thus, hydrogenation of **9** conducted in 96% ethanol in the presence of 10% palladium on charcoal at 2 atmospheres pressure afforded compound **10** in 90% yield as a single stereoisomer, as shown by ^{13}C NMR and GLC, with m.p. 90-95 °C (dec), $(\alpha)_D$ +9.49°. Choice of the solvent was crucial since the same reaction performed in ethyl acetate led to the formation of **14**, resulting from the selective reduction of the C-C double bond without hydrogenolysis of the benzyl ether, as deduced from its ^1H NMR spectrum: persistance of the benzyl protons at 4.5 ppm and absence of the olefinic proton. Reaction between **14** and boron trichloride in dichloromethane at -78 °C[7] gave **10** in 57% yield, allowing thus the deprotection of the primary alcohol. On the other hand, the use of W2 Ra-Ni in 96% ethanol gave **10** in only 17% yield among unidentified by-products.

In the next step of the synthetic sequence, reaction between tosylate **10** and sodium azide in DMF afforded azide **11** in 88% yield. This compound is an oil, $(\alpha)_D$ +163.6°, which decomposes on heating precluding a satisfactory microanalysis. In this reaction the epimer **15** (Scheme 2) was also produced as a minor product (isomer ratio 25:1). Both isomeric azides could be isolated by column chromatography , stereochemistry of the major compound **11** being assigned on the basis of its spectral data by comparison with other related products.[4]

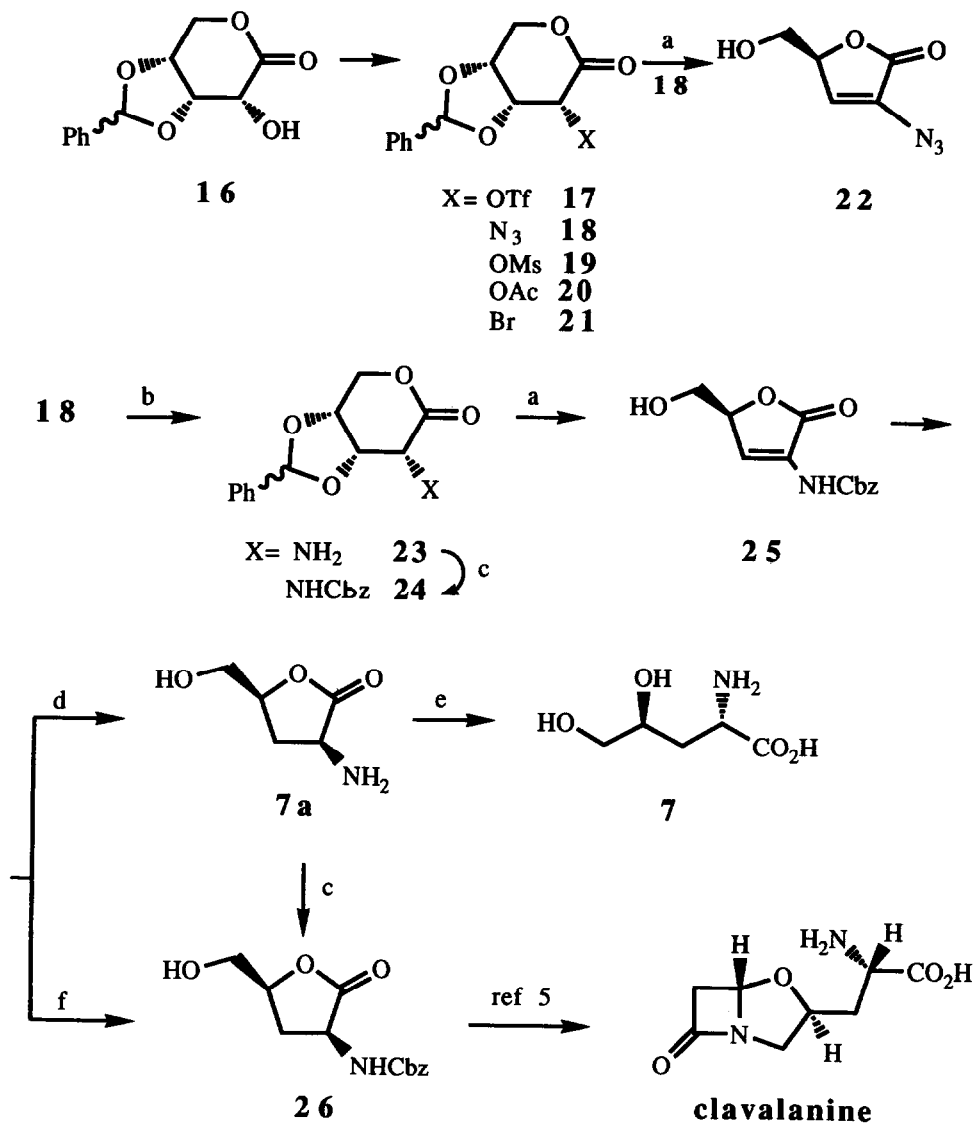
Finally, hydrogenation of **11** (10% palladium on charcoal in ethanol) led to the amino lactone **6a**. Attempts to obtain free erytho-amino acid **6** from **6a** failed and a syrup not suitable to be conveniently purified was obtained, thus preventing its characterization by physical and spectral



Reagents a: TsCl (2.5 eq), pyr. b: H_2, 10% Pd-C, 96% EtOH. c: NaN_3, DMF.
d: $PhCH_2OCOCl$, $NaHCO_3$, $THF-H_2O$

Scheme 2

data. In an alternative manner, crude amino lactone **6a** was reacted with benzyl chloroformate and excess sodium bicarbonate in THF-water to afford carbamate **12** as a solid, m.p. 120-122 °C, $(\alpha)_D$ +36.54°, which was fully characterized. Therefore, the synthesis of this amino lactone derivative, functionally and stereochemically equivalent to the amino acid **6**, was accomplished in 42% overall yield from 5-O-benzyl-D-ribonolatone, **8**.



Reagents. a: i) NaH, THF; ii) 1N HCl. b: H_2, 10% Pd-C, EtOAc. c: $PhCH_2OCOCl$, $NaHCO_3$, THF-H_2O. d: H_2, Ra-Ni (66% wt), EtOH e: Dowex 50W-X2 (H^+). f: H_2, Ra-Ni (33% wt), EtOH.

Scheme 3

4,5-Dihydroxy-D-erythro-L-norvaline, 7.

The synthetic sequence developed to prepare **7** and some lactonic derivatives is shown in Scheme 3.[8]

The first synthesis of clavalanine was reported in 1985 by a Hoffmann-La Roche group and involves the multistep preparation of the 4,5-dihydroxynorvaline derivative **26**, as a key intermediate, from D-xylose.[5] Later, compound **26** was prepared by Williams *et al.* by using an electrophilic glycine template obtained through resolution of a racemic suitable precursor.[9]

The stereospecific hydrogenation of butenolides prior or later to the introduction of a nitrogen group provides an easy and useful method to control the relative and absolute configuration of homochiral 2,4-disubstituted 1,4-lactones.[4,8] Thus, the synthesis of amino lactone **6a** described above involves hydrogenation of a tosyl derivative prior to displacement of tosylate group by azide anion. Actually, the synthesis of the title amino acid **7** could be assured through hydrogenation of butenolide **25** which is the key intermediate containing a protected amino function at the C-2 position. This compound was not described previous to our work, although Schmidt *et al.*[10] reported the synthesis of a (Z)-amino pentenoate which presumably would lead to butenolide **21** through acid hydrolysis.

The synthetic goal was carried out by using also D-ribonolactone, **1**, as a chiral precursor, as shown in Scheme 3. Fleet *et al.*[3] have reported the preparation of azide **18** from the earlier described alcohol **16**.[11] Hydrogenation of the azido group yielded quantitatively the amino lactone **23** which was easily converted into the new carbamate **24**, m.p. 129-131 °C, $(\alpha)_D$ -206° (84% yield). The obtention of the key intermediate **25** was realized through a one-pot base (NaH) induced elimination of benzaldehyde followed by ring contraction to give the 1,4-lactone **25**, m.p. 141-143 °C, $(\alpha)_D$ -3.8°, in 65% yield. This rearrangement probably takes place during the acid hydrolysis of the reaction mixture.

Hydrogenation of **25** in the presence of W2 Ra-Ni (66% weight of catalyst) in ethanol at 2 atmospheres pressure gave diastereospecifically the amino lactone **7a**, which was characterized as its hydrochloride, m.p. 195-200 °C (dec), $(\alpha)_D$ +18.0° (96% yield). Alternatively, chemoselective hydrogenation of the C-C double bond in **25** by using W2 Ra-Ni (33% weight of catalyst) afforded the N-carbamoyl derivative **26** in ca. 30% yield from D-ribonolactone, **1**. This compound was also prepared from amino lactone **7a** under reaction with benzyl chloroformate in the usual manner (Scheme 3). Physical constants of this product compare well with those previously described for the carbamate used as synthetic precursor of clavalanine[5]

(see Experimental Section). Thereby, a new formal total synthesis of this antibiotic was accomplished.

Finally, the open-chain amino acid **7** could be obtained by treating amino lactone **7a** with a sulfonic resin, giving a crystalline solid, m.p. 205-210 °C, $(\alpha)_D$ -19.5°, whose synthesis was achieved in 25% overall yield from **1**.

Therefore, the synthesis of the two title compounds, as well as those reported in ref. 4, illustrate the use of D-ribonolactone as a convenient chiral precursor in the sterocontrolled production of diastereomeric pairs of several non-protein natural or unnatural α-amino acids.

The overall elimination-rearrangement process that led to butenolide **25** from 1,5-lactone **20** seemed to be a promising method to prepare other butenolides bearing heteroatom-containing substituents at the C-2 position. However, reaction of the azido lactone **18** with sodium hydride furnished **22** in only 15% yield, among other unidentified materials (Scheme 3). Spectral data of this compound agree with those expected for the structure proposed: IR spectrum shows characteristic absorptions at 3500-3200 (OH), 2126 (N_3), and 1766 (C=O) cm^{-1}, and the olefinic proton appears as a doublet (J = 2.7 Hz) at 6.9 ppm in the ^1H NMR spectrum. Although several bases (NaH, DBU, LDA) and solvents were tried, unsatisfactory results were also obtained when the reaction was performed on lactones **17**, **19**, **20**,[13] and **21**, in which X is a triflate, mesylate, acetate or bromide substituent. Nevertheless, the process seems to work better when X is an alkoxy group.[12] Such results led us to conclude that this method is only useful when the substituent is stable enough in the reaction and work-up conditions. On the contrary, other competitive processes must lead to the production of undesired by-products.

EXPERIMENTAL SECTION

Melting points were determined on a hot stage and are uncorrected. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale). Electron-impact mass spectra were recorded at 70 eV.

Reaction of 5-O-benzyloxy-D-ribonolactone, 8, with tosyl chloride in pyridine: (S)-5-benzyloxymethyl-3-tosyloxy-2(5H)-furanone, 9, and 5-O-benzyl-2-O-tosyl-D-ribonolactone, 13.

A solution of **8** (3.3 g, 13.9 mmol), tosyl chloride (6.6 g, 34.6 mmol) in anhydrous pyridine (145 mL) was stirred first at 0 °C for 2 h and later at room temperature for 24 h. Then the reaction mixture was poured into

ethyl acetate (100 mL) and 5% HCl was added. After vigorous shaking the layers were separated and the organic phase was washed successively with 5% HCl. The combined aqueous phases were extracted with ethyl acetate and the combined organic extracts were dried and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (4:1 hexane-ethyl acetate as eluent) to afford the furanone **9** (2.3 g, 45% yield) and the saturated lactone **13** (0.9 g, 17% yield).

A mixture of the hydroxytosylate **13**, obtained in the preceding reaction, acetic anydride (2 mL, 21.2 mmol) and anhydrous pyridine (10 mL) was stirred at room temperature overnight. The reaction mixture was worked-up as above giving, after purification by column chromatography, 0.4 g (94%) of butenolide **9** (60% total yield from **8**).

Compound 9: crystals, m.p. 54-56 °C (from ether-hexane); $(\alpha)_D$ -83.3° (c = 1.5, $CHCl_3$); IR (KBr) 1778, cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) 2.44 (3 H, s), 3.74 (1 H, dd, J = 11.0 Hz, J' = 4.3 Hz), 3.85 (1 H, J = 11.0 Hz, J' = 3.5 Hz), 4.53 (2 H, s), 5.30 (1 H, ddd, J = 4.3 Hz, J' = 3.5 Hz, J'' = 2.2 Hz), 7.1 (1 H, d, J = 2.2 Hz), 7.33 (5 H, m), 7.42 (2 H, d, J = 8.9 Hz), 7.85 (2 H, d, J = 8.9 Hz); 20 MHz ^{13}C NMR ($CDCl_3$) 21.4, 69.0, 76.9, 78.5, 127.5, 127.7, 128.3, 129.8, 131.4, 133.3, 137.1, 146.3, 165.0; MS, m/e (%) 219 (M - Ts, 7), 91 (100). Anal. Calcd. for $C_{18}H_{19}O_6S$: C, 61.02; H, 4.85; S, 8.57. Found: C, 60.83; H, 4.87; S, 8.52.

Compound 13: crystals, m.p. 75-77 °C (from ether-hexane); $(\alpha)_D$ -46.75° (c = 1.54, $CHCl_3$); IR (KBr) 1778 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) 2.44 (3 H, s), 3.77 (1 H, dd, J = 11.0 Hz, J'2.4 Hz), 3.85 (1H, dd, J = 11.0 Hz, J' = 2.4 Hz), 4.48 (1 H, dd, J = 4.9 Hz, J' = 4.3 Hz), 4.54 (2 H, s) 4.58 (1 H, m), 5.11 (1 H, d, J = 4.3 Hz), 5.32 (1 H, d, J = 4.9 Hz), 7.33 (5 H, m), 7.4 (1 H, d, J = 8.5 Hz), 7.74 (1 H, d, J = 8.5 Hz); 20 MHz ^{13}C NMR ($CDCl_3$) 21.4, 68.7, 69.8, 73.6, 74.2, 83.9, 127.5, 128.0, 128.4, 129.8, 131.5, 136.8, 145.6, 169.5; MS, m/e (%) 237 (M - Ts, 1), 91 (100), 65 (18), 45 (15), 43 (19). Anal. Calcd. for $C_{19}H_{20}O_7S$: C, 58.22; H, 5.14; S, 8.18. Found: C, 57.97; H, 5.28; S, 7.94.

(3S,5S)-5-Hydroxymethyl-3-tosyloxy-2(3H)-dihydrofuranone, 10.

(i) By hydrogenation of compound 9: Butenolide **9** (500 mg, 1.34 mmol) in 96% ethanol (30 mL) was hydrogenated in the presence of 10% Pd-C (50 mg) at 2 atmospheres pressure and at room temperature for 16 h. The mixture was filtered through celite and the solvent was evaporated to afford a residue which was chromatographed on silica gel (3:1 hexane-ethyl acetate as eluent) to give product **10** (340 mg, 89% yield).

(ii) From 9 through the ether 14: Operating as above but using only etyl acetate as a solvent, 239 mg of **14** was obtained from **9**. Then, boron trichloride (1.5 mL of a 1 M sol in dichloromethane, 1.5 mmol) was added to a solution of ether **14** (114 mg, 0.3 mol) at -78 °C. After stirring for 3 h, a 1:1 mixture of methanol-dichloromethane (20 mL) was added and the solution was stirred at room temperature for 1.5 h. The solvents were removed at reduced pressure and the residue was chromatographed on silica gel (1:3 hexane-ethyl acetate as eluent) to afford 49 mg (57% yield) of **10**. Crystals, m.p. 90-95 °C (dec) (from ether-hexane); $(\alpha)_D$ +9.49° (c = 1.18, $CHCl_3$); IR (KBr) 3600-3100, 1792 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) 1.84 (1 H, br s), 2.40 (1 H, ddd, J = 13.3 Hz, J' = 10.7 Hz, J'' = 4.0 Hz), 2.44 (3 H, s), 2.65 (1 H, ddd, J = 13.3 Hz, J' = 9.3 Hz, J'' = 5.3 Hz), 3.62 (1 H, dd, J = 10.7 Hz, J' = 5.3 Hz), 3.92 (1 H, dd, J = 10.7, J' = 5.3 Hz), 4.49 (1 H, m), 5.17 (1 H, dd, J = 10.7 Hz, J' = 9.3 Hz), 7.35 (2 H, d, J = 8.5 Hz), 7.84 (2 H, d, J = 8.5 Hz); 20 MHz ^{13}C NMR (acetone-d_6) 21.5, 62.8, 75.0, 78.2, 128.7, 130.8, 134.0, 146.3, 171.0; MS, m/e (%) 287 (M + 1, 1), 286 (M, 5), 173 (21), 155 (45), 91 (100), 65 (34). Anal. Calcd. for $C_{12}H_{14}O_6S$: C, 50.40; H, 4.93; S, 11.21. Found: C, 50.19; H, 5.02; S, 11.00.

Reaction of 10 with sodium azide.

A light-protected solution of **10** (380 mg, 1.3 mmol) and sodium azide (220 mg, 3.4 mmol) in anhydrous DMF (11 mL) was stirred at room temperature for 5 days. Then ethyl acetate (50 mL) was added and the resulting mixture was washed successively with water and brine, and dried. The solvent was evaporated at reduced pressure and the residue was chromatographed on silica gel (3:1 hexane ethyl acetate as eluent) to give compounds **11** (177 mg) and **15** (7 mg), in 88% total yield. These products are oils which decompose under heating when distillation was attempted.

(3R,5S)-3-Azido-5-hydroxymethyl-2(3H)-dihydrofuranone, 11: $(\alpha)_D$ +163.6° (c = 1.32, $CHCl_3$); IR (film) 3750-3100, 2116, 1778 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) 2.05 (1 H, br s), 2.15 (1 H, ddd, J = 13.4 Hz, J' = 8.5 Hz, J'' = 3.7 Hz), 2.50 (1 H, ddd, J = 13.4 Hz, J' = 9.1 Hz, J'' = 3.7 Hz), 3.63 (1 H, dd, J = 12.2 Hz, J' = 2.4 Hz), 3.95 (1 H, dd, J = 12.2 Hz, J' = 2.4 Hz), 4.50 (1 H, m), 4.65 (1 H, m); 20 MHz ^{13}C NMR ($CDCl_3$) 30.3, 57.2, 63.5, 78.9, 174.5; MS, m/e (%) 158 (M + 1, 1), 129 (M - N_2, 7), 57 (100), 42 (M - N_3, 88).

(3S,5S)-3-Azido-5-hydroxymethyl-2(3H)-dihydrofuranone, 15: IR (film) 3660-3090, 2116, 1780 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) 1.92 (1 H, br s), 2.10 (1 H, ddd, J = 13.4 Hz, J' = 10.4 Hz, J'' = 6.7 Hz), 2.53 (1 H, ddd, J = 13.4 Hz, J' = 9.1 Hz, J'' = 6.1 Hz), 3.65 (1 H, dd, J = 12.8 Hz, J' = 4.9 Hz), 3.93 (1 H, dd, J = 12.8 Hz, J' = 3.0 Hz), 4.37 (1 H, dd, J = 11.0 Hz, J' = 9.1 Hz), 4.54 (1 H, m).

(3R,5S)-3-Benzyloxycarbonylamino-5-hydroxymethyl-2(3H)-dihydrofuranone, 12.

Azide **11** (150 mg, 1 mmol) in 96% ethanol (10 mL) was hydrogenated in the presence of 10% Pd-C (20 mg) at atmospheric pressure and at room temperature for 1 h. The reaction mixture was filtered through celite and the solvent was removed to dryness. The residue was poured into 1:1 THF-water (20 mL), the resulting solution was ice-cooled and then sat aqueous sodium bicarbonate (5 mL) and benzyl chloroformate (0.40 mL, 2.4 mmol) were added. The mixture was stirred at 0 °C for 30 min and at room temperature for further 30 min. Water (10 mL) was the added and the layers were separated. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried and the solvent was removed. The residue was chromatographed on silica gel (3:1 hexane-ethyl acetate as eluent) to furnish carbamate **12** (219 mg, 86% yield). Crystals m.p. 120-122 °C (from ether-hexane); $(\alpha)_D$ +36.54° (c = 0.26, methanol); IR (KBr) 3413, 3325, 1781, 1681 cm^{-1}; 400 MHz ^1H NMR (acetone-d_6) 2.39 (1 H, br s), 2.44 (1 H, ddd, J = 12.2 Hz, J' = 3.8 Hz, J'' = 1.9 Hz), 2.55 (1 H, ddd, J = 12.2 Hz, J' = 10.3 Hz, J'' = 2.3 Hz), 3.69 (1 H, ddd, J = 5.6 Hz, J' = 3.8 Hz, J'' = 1.9 Hz), 3.82 (1 H, ddd, J = 5.6 Hz, J' = 3.8 Hz, J'' = 1.9 Hz), 4.38 (1 H, m), 4.65 (1 H, m), 5.09 (2 H, s), 6.87 (1 H, br s), 7.34 (5 H, m); 20 MHz ^{13}C NMR (acetone-d_6) 50.4, 64.0, 66.4, 74.7, 77.7, 128.6, 129.2, 130.9, 137.9, 156.6, 175.2; MS, m/e (%) 265 (M, 2), 108 (36), 91 (100), 65 (19). Anal. Calcd. for $C_{13}H_{15}O_5N$: C, 58.92; H, 5.71; N, 5.29. Found: C, 58.63, H, 5.80; N, 5.08.

3,4-O-Benzylidene-2-O-methanesulphonyl-1,5-D-ribonolactone, 19.

Methanesulphonyl chloride (2.0 mL, 25 mmol) was added to a stirred solution of alcohol **16** (5.6 g, 24 mmol) in anhydrous pyridine (25 mL) at -15 °C and the mixture was stirred at this temperature for 30 min and at 0 °C for 1.5 h. Then water (75 mL) was added and the mixture was stirred at 0 °C for 30 min; the produced precipitate was filtered and washed successively with 5% HCl, water and hexane. The solid was dried under vacuo affording mesylate **19** (7.0 g, 94% yield); crystals, m.p. 153-155 °C (from

ethyl acetate-hexane); $(\alpha)_D$ -151.0° (c = 1.80, acetone); IR (KBr) 1760 cm^{-1}; 80 MHz ^1H NMR (acetone-d_6) 3.3 (3 H, s), 4.5 (1 H, dd, J = 12.5 Hz, J' = 1.4 Hz), 4.8 (1 H, dd, J = 12.5 Hz, J' = 1.7 Hz), 4.9 (1 H, ddd, J = 8.2 Hz, J and J' c.a. 1.5 Hz), 5.1 (1 H, dd, J = 8.2 Hz, J' = 3.2 Hz), 5.7 (1 H, d, J = 3.2 Hz), 5.9 (1 H, s), 7.5 (5 H, complex abs); 20 MHz ^{13}C NMR (DMSO-d_6) 38.5, 67.3, 73.4, 74.6, 75.0, 103.2, 127.0, 128.2, 130.0, 135.4, 166.0; MS, m/e (%) 315 (M + 1, 3), 314 (M, 7), 313 (M - 1, 9), 129 (29), 105 (100), 97 (13), 91 (13), 79 (47). Anal. Calcd. for $C_{13}H_{14}O_7S$: C, 49.67; H, 4.50; S, 10.20. Found: C, 49.50; H, 4.55; S, 10.21.

2-Bromo-2-deoxy-3,4-O-benzylidene-1,5-D-ribonolactone, 21.

A light-protected mixture of mesylate **19** (1.6 g, 4.2 mmol) and NaBr (1.3 g, 12.6 mmol) in acetone (45 mL) was stirred at room temperature for 3 days. The solvent was removed, the residue was poured into ethyl acetate (125 mL) and washed successively with sat aqueous sodium thiosulphate and with brine. The organic phase was dried and the solvent was evaporated at reduced pressure. Bromide **21** was crystallyzed by addition of ethyl acetate to the reaction crude. The mother liquors were concentrated and chromatographed on silica gel using mixtures of hexane-ethyl acetate as eluents. In this way, 0.9 g (73% yield) of pure **21** was obtained; crystals, m.p. 142-145 °C (dec); $(\alpha)_D$ -70.5° (c = 1.90, acetone); IR (KBr) 1744 cm^{-1}; 400 MHz ^1H NMR (acetone-d_6) 4.6 (1 H, d, J = 2.0 Hz), 4.7 (1 H, dd, J = 13.3 Hz, J' = 1.4 Hz), 4.8 (1 H, dt, J = 8.0 Hz, J' = 1.8 Hz), 4.9 (1 H, dd, J = 13.3 Hz, J' = 1.8 Hz), 5.0 (1 H, dd, J = 8.0 Hz, J' = 2.0 Hz), 5.8 (1 H, s), 7.5 (5 H, s); 100 MHz ^{13}C NMR (acetone-d_6) 38.1, 69.1, 72.3, 78.0, 104.6, 128.0, 129.2, 130.8, 136.6, 165.4. Anal. Calcd. for $C_{12}H_{11}BrO_4$: C, 48.18; H, 3.71. Found: C, 47.97; H, 3.66.

3,4-O-Benzylidene-2-benzyloxycarbonylamino-2-deoxy-1,5-D-ribonolactone, 24.

Azide **18** (220 mg, 0.8 mmol) in ethyl acetate (20 mL) was hydrogenated in the presence of 10% Pd-C (49 mg) at atmospheric pressure and at room temperature for 2.5 h. The reaction mixture was filtered trough celite and the solvent was removed under vacuo. The oily residue, that contains amine **23**, was poured into 3:1 water-THF and sodium bicarbonate (308 mg, 3.7 mmol) and benzyl chloroformate (0.45 mL of a 50% toluene solution, 1.3 mmol) were added to the ice-cooled resultant solution. The mixture was vigorously stirred at 0 °C for 30 min and at room temperature for 2 h; pH was maintained in 7-8 range through addition of sat aqueous sodium bicarbonate. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried and the solvents were evaporated at reduced pressure. The crude was chromatographed on silica gel (1:1 hexane-ethyl acetate as eluent) to afford 260 mg (84% yield) of carbamate **24**. Crystals, m.p. 129-131 °C (from ethyl acetate-hexane); $(\alpha)_D$ -206.0° (c = 3.80, $CHCl_3$); IR (KBr) 1740, 1690 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$) 4.3 (1 H, dd, J = 12.9 Hz, J' = 1.3 Hz), 4.5-4.7 (3 H, complex abs), 4.9 (1 H, dd, J = 7.7 Hz, J' = 3.2 Hz), 5.1 (2 H, s), 5.7 (1 H, s), 5.9 (1 H, br s), 7.3 (5 H, s), 7.4 (5 H, s); 20 MHz ^{13}C NMR ($CDCl_3$) 52.7, 67.1, 72.9, 104.0, 127.0, 128.0, 128.3, 130.0, 134.6, 135.8, 155.7, 168.2; ^{13}C NMR (acetone-d_6) 53.8, 67.1, 68.0, 74.5, 76.4, 104.4, 128.1, 128.4, 128.6, 128.9, 129.1, 130.6, 136.9, 137.8, 156.8, 169.5; MS, m/e (%) 369 (M, 0.3), 368 (M - 1, 1.2), 91 (100); Anal. Calcd. for $C_{20}H_{19}NO_6$: C, 65.04; H, 5.15; N, 3.79. Found: C, 65.01; H, 5.14; N, 3.68.

(S)-3-Benzyloxycarbonylamino-5-hydroxymethyl-2(5H)-furanone, 25.

Sodium hydride (40 mg of a 60% suspension in oil, 1 mmol) was added to a solution of **24** (204 mg, 0.55 mmol) in anhydrous THF (4 mL) previously

cooled at -20 °C; the mixture was stirred at -20 °C for 30 min, and then 1N HCl was slowly added until pH acid. The resulting solution was successively stirred at room temperature for 15 min, saturated with sodium chloride and extracted with ethyl acetate. The combined organic extracts were dried and the solvent was removed at reduced pressure. The residue was crystallized from hexane-ether-ethyl acetate giving crystalline butenolide **25** (72 g). The mother liquors were concentrated and chromatographed on silica gel (1:1 hexane-ethyl acetate as eluent) to afford 96 mg of **25** (66% total yield); m.p.141-143 °C; $(\alpha)_D$ -3.8° (c = 2.60, acetone); IR (KBr) 3320, 1765, 1730, 1670 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$) 1.8 (1 H, br s), 3.7 (1 H, dd, J = 12.9 Hz, J' = 5.2 Hz), 4.0 (1 H, dd, J = 12.9 Hz, J' = 4.0 Hz), 5.1 (1 H, m), 5.2 (2 H, s), 7.1 (1 H, br s), 7.3 (1 H, d, J = 3.4 Hz), 7.4 (5 H, s); 20 MHz ^{13}C NMR (methanol-d_4) 61.4, 66.3, 81.8, 126.2, 127.2, 127.6, 127.9, 128.3, 136.3, 153.6, 168.4; MS, m/e (%) 264 (M + 1, 0.7), 263 (M, 4.6), 91 (100); Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.94; N, 5.32. Found: C, 59.45; H, 5.02; N, 5.20.

Total hydrogenation of 25: compound 7 and its hydrochloride.

Butenolide **25** (160 mg, 0.6 mmol) in ethanol (5 mL) was hydrogenated in the presence of W2 Ra-Ni (230 mg) at 2 atmospheres pressure and at room temperature for 15 h. The suspension was decanted and the catalyst was washed with ethanol. The solvent was removed under vacuo and the residue was poured into ethyl acetate. The resulting colloidal suspension was filtered through celite and the solvent was evaporated. The oily residue was poured into 1N HCl (5 mL) and the solution was stirred at room temperature for 30 min, and then passed through a Dowex 50Wx2 resin, using successively water and 0.3N NH_4OH as eluents, to afford **amino acid 7** (57 mg, 64% yield) which is a solid, m.p. 205-210 °C (dec); $(\alpha)_D$ -19.5° (c = 1.70, water); IR (KBr) 3500-2400, 1610, 1595 cm^{-1}; 80 MHz ^1H NMR (D_2O) 2.9 (2 H, t, J = 5.7 Hz), 3.4-3.9 (4 H, complex abs); 100 MHz ^{13}C NMR (D_2O) 33.4, 53.5, 66.1, 69.7, 175.4.

Amino acid **7** (30 mg, 0.2 mmol) in HCl sat methanol (10 mL) was stirred at room temperature for 1 h. The solvent was removed at reduced pressure to give an oil which was crystallized from ethanol-ether affording **(3S,5S)-3-amino-5-hydroxymethyl-2(3H)-dihydrofuranone hydrochloride** (32 mg, 96% yield); m.p. 195-200 °C (dec); $(\alpha)_D$ +18.0° (c = 1.60, water); IR (KBr) 3250-2500, 1775 cm^{-1}; 80 MHz ^1H NMR (D_2O) 2.1 (1 H, q, J = 11.3 Hz), 2.6 (1 H, m), 3.5 (1 H, ddd, J =12.0 Hz, J' = 6.0 Hz, J'' = 3.2 Hz), 3.9 (1 H, dd, J = 12.0 Hz, J' = 3.2 Hz), 4.4 (1 H, dt, J = 11.3 Hz, J' = 8.5 Hz); 100 MHz ^{13}C NMR (D_2O) 28.8, 50.4, 62.5, 81.0, 174.5.

(3S,5S)-3-Benzyloxycarbonylamino-5-hydroxymethyl-2(3H)-dihydrofuranone, 26.

Butenolide **21** (120 mg, 0.4 mmol) was hydrogenated as described above. The reaction crude was made to react with benzyl chloroformate and sodium bicarbonate in THF following the same procedure than that described for amine **19**, affording carbamate **23** (82 mg, 68% yield); crystals, m.p. 114-115 °C (from ether); $(\alpha)_D$ +3.6° (c = 1.60, methanol) (lit.[5] m.p. 112-115 °C (from ether), $(\alpha)_D$ +3.3° (c = 1.14, methanol)); IR and ^1H NMR spectral data are in accordance with those described for **26** in ref 5.

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