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ENANTIOSELECTIVE SYNTHESIS OF HYDROXY α-AMINO ACIDS. (-)-erythro- and (-)-threo-γ-HYDROXYNORVALINES.

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Abstract.- The amino acids (-)-erythro- and (-)-threo-γ-hydroxynorvaline have been synthesized from D-ribonolactone, **6**, as single chiral precursor. Moreover, β-hydroxy-α-azido-γ-valerolactones **12a** and **12b** have been also prepared from **6** in two different alternative ways. These compounds afford β,γ-dihydroxy-α-amino acids **18a** and **18b** with D-arabino and D-ribo configuration, respectively.

INTRODUCTION

Since 1961, when Greenstein and Winitz[1] listed some ninety amino or imino acids of non-protein origin, the number of this kind of known compounds has dramatically increased. Such products are those amino acids which are not found in protein main chains either for lack of a specific transfer RNA and codon triplet or because they do not arise from protein amino acids by post-translatorial modification.[2] In any case, the range and variety of structures found reflect the great diversity of organism metabolisms.

Those α-amino acids containing one or more hydroxyl groups are an important class of naturally occurring products. Thus, variously substituted β-hydroxy-α-amino acids are interesting compounds both as constituents of biologically active non-protein peptides,[3] and as precursors of amino poliols and β-lactam antibiotics.[4] On the other hand, α-amino acids with a hydroxyl group in γ position have also been obtained from natural sources.[5] In particular, γ-hydroxynorvaline, **1**, (Chart 1) has been isolated for the first time by Fowden[6] from the seeds of Lathyrus odoratus (Papilionaceae) as a mixture of diastereoisomers, a fact attributed by this author to a partial racemization during the isolation process. Some years later, Matzinger et al.[7] isolated a mixture of erythro- and threo-γ-hydroxynorvalines from the carpophores of Boletus Satanas Lenz (Basidiomycetae), showing the natural origin of both isomers. Their chirality was determined using chiroptical methods and by correlation of the separated erythro and threo natural products with synthetic **2** and **3** (its enantiomer), prepared from (-)-γ-valerolactona, **5**, which in turn was obtained in 69% optical purity through

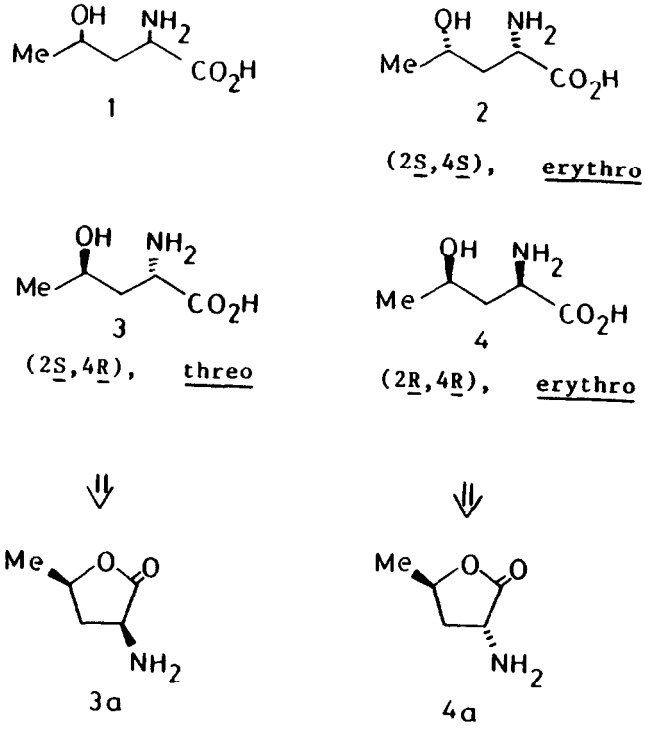
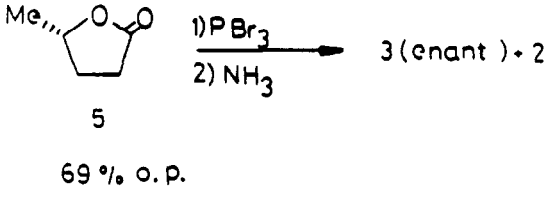


Chart 1

resolution of the racemate (Scheme 1). Moreover, further studies revealed that optical purity of the natural threo-isomer is 88% (2S,4R), **3**, whereas erythro-isomer exists as a partial racemate **2/4** in a 3:2 ratio.



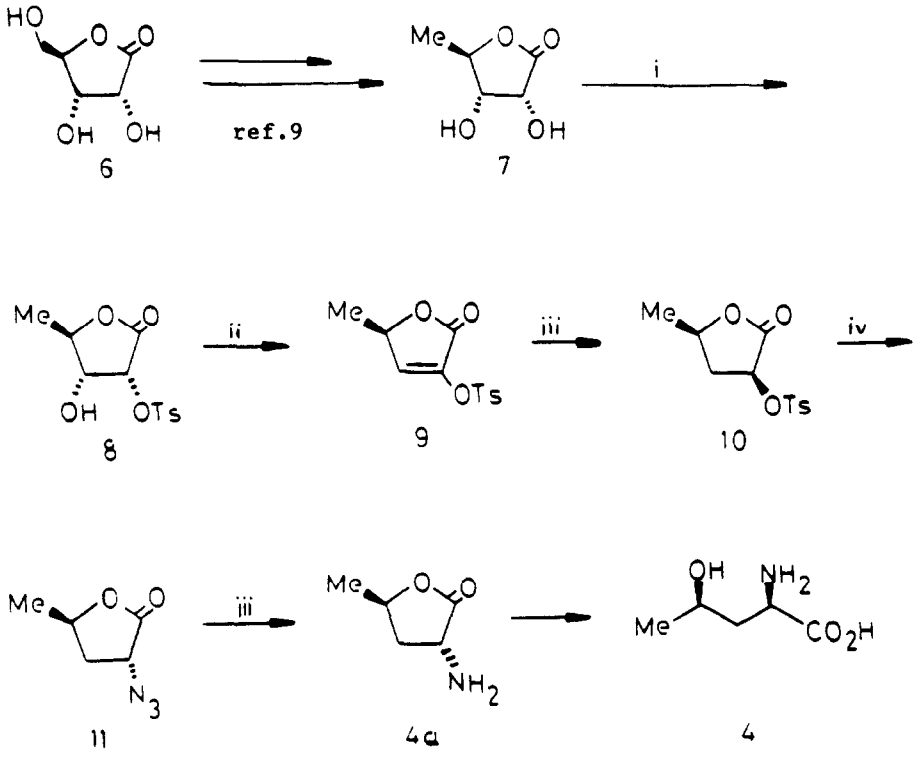
Scheme 1

As far as we know, only one synthesis of racemic erythro- and threo-**1** has been recently published, the key step involving the mercuric-ion initiated cyclization of a carbamoyl ether.[8] In this article we report the first total enantio- and diastereocontrolled synthesis of (2S,4R)- and

(2R,4R)-γ-hydroxynorvaline, **3** and **4** respectively, from D-ribonolactone, **6**, as a single chiral precursor. The strategy assumed to achieve the synthetic goals lies in developping convenient methods to prepare lactones **3a** and **4a**, that are equivalent to the respective amino acids **3** and **4** (Chart 1), the chirality of D-ribonolactone being transferred to the target molecules at C-4 position, and has been used to induce the configuration at C-2, by means of stereocontrolled transformations.

RESULTS AND DISCUSSION

5-Deoxy-D-ribonolactone, **7**, (Scheme 2) easily prepared from **6**,[9] has been selectively converted into the tosylate **8**, m.p. 130-132° C, $[\alpha]_D$ -8.8°



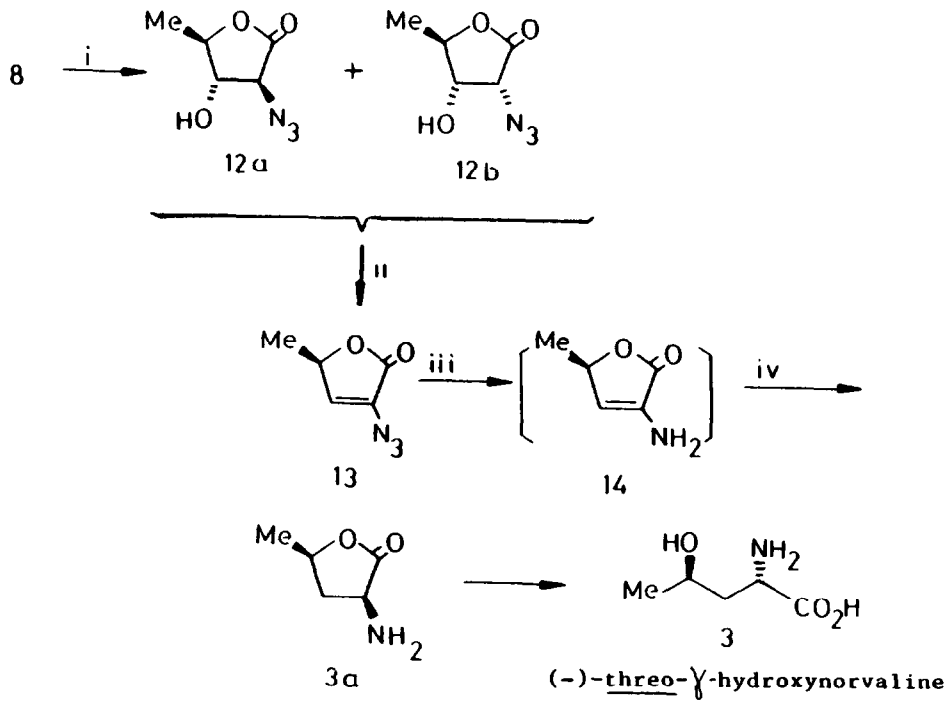
Reagents: i) TsCl, pyr. ii) Ac_2O, pyr. iii) H_2, Pd/C.
iv) NaN_3, DMF.

Scheme 2

in 83% yield, by slow addition of 1 eq of tosyl chloride at 0° C. Compound **8** is the common precursor of amino acids **3** and **4**, through divergent synthetic routes.

The route leading to (2R,4R)-erythro-γ-hydroxyvaline, **4**, (Scheme 2) starts with the reaction of tosylate **8** with acetic anhydride in pyridine, affording quantitatively the butenolide **9**, m.p. 58-59° C, $[\alpha]_D$ -32.7°, by *in situ* elimination of acetic acid from the acetyl derivative intermediate. Subsequent stereospecific hydrogenation of **9** at 2 atmospheres pressure, in the presence of 10% palladium on charcoal as catalyst, yielded quantitatively the saturated tosylate **10** as an oil, $[\alpha]_D$ +16.7°. Reaction of **10** with sodium azide in DMF led to the stereoselective formation of liquid azide **11**, as a single isomer, $[\alpha]_D$ +221.0° in 94% yield, that exhibited only one set of carbon signals in the cmr spectrum, and whose relative configuration was supported by pmr spectroscopic data, by comparison with related compounds.[7] Finally, catalytic hydrogenation of **11** followed by treatment of the reaction crude with hydrochloric acid afforded the amino lactone **4a**, characterized as the hydrochloride derivative, m.p. 164-167° C (dec), $[\alpha]_D$ +41.0°. Filtration of **4a** through a sulphonic Dowex resin gave the free erythro-amino acid **4**, m.p. 192-194° C, $[\alpha]_D$ -35.2°, in 65% overall yield from 5-deoxy-D-ribonolactone, **7**. Physical and spectroscopic data of both **4** and **4a** are in accordance to those reported for the natural product.[7]

The second synthetic route allows the synthesis of (2S,4R)-threo-hydroxynorvaline, **3**, and is very similar to the former, explained above. Actually, the order of the transformations involving (a) an elimination process to give a butenolide, and (b) displacement of the tosyloxy group by azide anion, is reversed in order to induce the right configuration of isomer **3**. (Scheme 3). Therefore, the tosylate **8** was made to react with sodium azide in DMF, at room temperature for 5 days, leading to a 7:3 mixture of diastereoisomeric azides **12a/12b**, that could be chromatographically isolated and characterized by their spectroscopic data and optical rotations. This result contrasts with the reaction of tosylate **10** with sodium azide in similar conditions, that afforded stereoselectively only one isomer. The mixture **12** gave the unsaturated azide **13** as a liquid, $[\alpha]_D$ -73.6°, when treated with acetic anhydride in pyridine. Compound **13** underwent catalytic hydrogenation in different conditions. Thus, hydrogenation at atmospheric pressure in ethyl acetate as solvent and using 10% Pd/C afforded quantitatively the enamine **14** as an unstable liquid. The pmr spectrum showed a signal for the olefinic proton at δ 5.9 as a doublet, J = 1.33 Hz; (c.f. with azide **13**, δ 6.56, d, J = 1.33 Hz). Both **14** and **13** under Ra-Ni hydrogenation, in ethanol at atmospheric pressure, yielded **3a** that was converted into the open-chain amino acid **3**, m.p. 194-196° C, $[\alpha]_D$ =



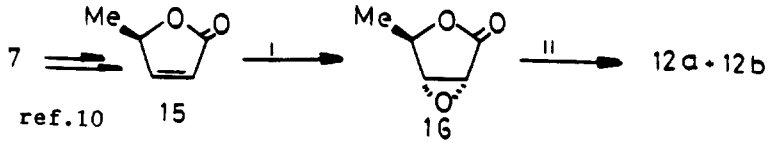
Reagents: i) NaN_3, DMF. ii) Ac_2O, pyr. iii) H_2, Pd/C. iv) H_2, Ra-Ni.

Scheme 3

30.5°. (Lit[7] m.p. 194-195° C, $\{\alpha\}_D$ -35.5°).

In this way, threo-**3** was synthesized in 65% overall yield from the hydroxy lactone **7**.

The intermediate hydroxy azides **12a** and **12b** are interesting products that can serve as chiral precursors in the synthesis of β-hydroxy-α-amino acids, and for this reason we decide to study the factors that can influence their formation. We have recently reported[10] that reactions of (+)-β-angelica lactone epoxide, **16**, (Scheme 4) with several nucleophiles take place regioselectively at the α-carbonyl position. Moreover, the obtention of 1,2-hydroxyazides by reaction of epoxides with sodium azide[11] or hydrazoic acid[12] have been described in the literature. Therefore, we studied the use of **16** as a suitable precursor to prepare azides **12**, but, in our case, the epoxy lactone **16** remained unaltered when treated with sodium azide in DMF. This result agrees with the low reactivity of **16** with



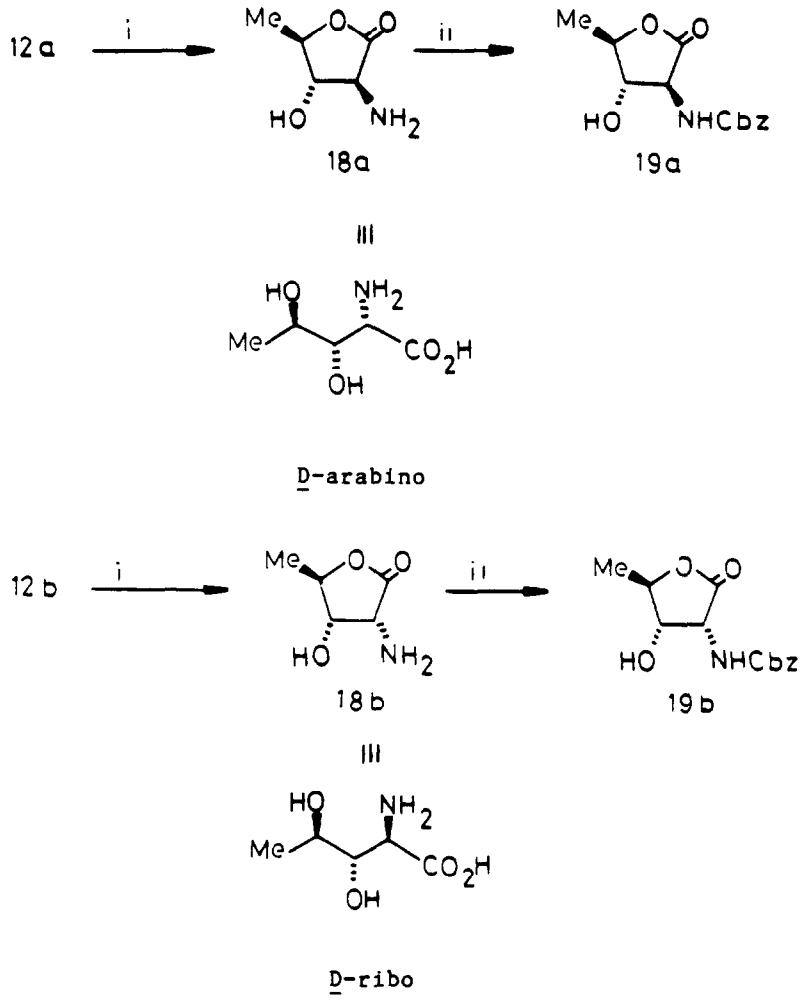
Reagents: i) NaOCl, pyr. ii) Me_3SiN_3, MeOH.

Scheme 4

nucleophiles in neutral or basic medium observed in our previous work.[10] In contrast, reaction of **16** with hydrazoic acid, generated *in situ* from trimethylsilyl azide and methanol, in DMF at room temperature for 72 h, led to a 91:9 mixture of diastereoisomeric azides **12a/12b** in 70% yield. The formation of the minor product **12b** can be rationalized assuming an equilibrium process of the epimeric azides in the reaction conditions. Several experiments, conducted at different temperature and time conditions, allowed the estimation of the equilibrium ratio of these isomers as 70:30, the same distribution found in the reaction of tosylate **8** with sodium azide in the conditions described above. Since product **12a** was recovered unaltered after stirring in DMF for 4 days, and a mixture of **12a/12b** in a 20:80 initial proportion[13] was converted into a 70:30 mixture of these diastereoisomers by treatment with sodium azide, the role of azide anion as epimerization promotor was then evidenced.

Although the participation of the *vic*-hydroxyl group has not been established, the influence of such a function in this process was evidenced by our own results, by comparing the formation reactions of azido derivatives from tosylate **8** and epoxide **16**, with that from tosylate **10** , and is also supported by literature data. For instance, Godefroi has reported the reaction of mesyl derivatives of several 2-hydroxybutyrolactones to occur in highly stereoselective manner, affording the azides that result of a S_N2-type displacement of mesyloxy group by azide ion.[14] Nevertheless, Lundt *et al.* have reported the obtention of diastereoisomeric mixtures of hydroxy azides in the reactions of different 2-bromo-3-hydroxybutyrolactones with sodium azide.[15] All these results show thus the different behaviour of these azido butyrolactones in the presence or in the absence of a *vic*-hydroxy substituent.(See Table 1)

The azides **12a** and **12b** are precursors of β,γ-dihydroxy-α-amino acids **18a** and **18b**, with configuration *D*-arabino and *D*-ribo, respectively. Thus, hydrogenation of **12a** using 10% Pd/C in ethyl acetate gave amino lactone **18a**,



Reagents: i) H_2, Pd/C. ii) $ClCO_2Bz$, $NaHCO_3$.

Scheme 5

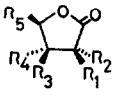
that by reaction with benzyl chloroformate afforded the N-benzyl derivative **19a**, m.p. 144-146° C, $[\alpha]_D$ +56.4°, in 87% overall yield. Similarly, azide **12b** yielded carbamate **19b**, m.p. 135-137° C, $[\alpha]_D$ -8°.[16]. (Scheme 5).

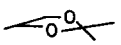
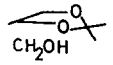
Since the two enantiomers of β-angelica lactone epoxide are easily synthesized[10b] the availability of both series of hydroxy amino acids,

18a/18b and their enantiomers rests assured, showing the versatility of this last synthetic way.

Table 1. Reaction products of some γ-lactone derivatives with azide anion.

Substrat	Product(s) (% ratio)	Ref.
8	**12a** (70) + **12b** (30)	This work
10	**11** (100)	Id.
16	**12a** (70) + **12b** (30)	Id.
20	**23** (100)	14
21	**24** (50) + **25** (50)	15
22	**26** (50) + **27** (50)	15



	R_1	R_2	R_3	R_4	R_5
20	OMs	H	H	H	
21	H	Br	OH	H	CH_2OH
22	Br	H	H	OH	CH_2OH
23	H	N_3	H	H	
24	N_3	H	OH	H	CH_2OH
25	H	N_3	OH	H	CH_2OH
26	N_3	H	H	OH	CH_2OH
27	H	N_3	H	OH	CH_2OH

EXPERIMENTAL SECTION

Melting points have been determined on a Kofler hot stage and are uncorrected. Optical rotations were obtained on a Propol polarimeter, model Dr. Kernchen. The 70 eV electron impact mass spectra were recorded on a Hewlett-Packard spectrometer model 5985B. The ir spectra were obtained on a Nicolet ZDX apparatus. The 80 MHz pmr and the 20 MHz cmr spectra were recorded on a Bruker spectrometer model WP 80 SY, and the 400 MHz pmr and 100 MHz cmr spectra on a Bruker AM-400 WB; chemical shifts are given in parts per million relative to TMS (δ scale); in the spectra from aqueous solutions, water was centered at 4.6 ppm. Microanalyses were performed at the Instituto de Química Bio-Orgánica, C.S.I.C., Barcelona.

(-)-2-O-Tosyl-5-deoxy-γ-D-ribonolactone, 8.

To a stirred and ice-cooled solution of 5-deoxy-γ-D-ribonolactone, **7**,[7] (0.50 g, 3.78 mmol) in anhydrous pyridine (10 ml), tosyl chloride (0.72 g, 3.78 mmol) was slowly added. The mixture was further stirred at 0° C for 30 min and allowed to stand at -20° C overnight. Then, ethyl acetate (100 ml) and 5% HCl (25 ml) were added and the layers separated. The organic phase was washed with 5% HCl and dried over sodium sulfate. The solvent was removed at reduced pressure and the residue was flash-chromatographed on silica gel, using 3:1 hexane ethyl acetate as eluent, affording 0.89 g (92% yield) of tosylate **8**, m.p. 130-132° C (from chloroform-hexane), $[\alpha]_D$ -8.8° (c 2.73 in MeOH); ir (KBr): 3560, 3300, 2960-2940, 1760, 1590, 1460, 1370, 1320, 1300, 1280, 1200, 1100, 1080, 1030 cm^{-1}; pmr ($CDCl_3$): 1.43 (d, J=6.7 Hz, 3H); 2.47 (s, 3H); 2.63 (broad s, 1H); 4.40 (dd, J=5.3 Hz, J'=1.3 Hz, 1H); 4.7 (dq, J=6.7 Hz, J'=1.3 Hz, 1H); 5.13 (d, J=5.3 Hz, 1H), 7.4 (d, J=8.0 Hz, 2H); 7.7 (d, J=8.0 Hz, 2H); cmr ($CDCl_3$): 13.9, 21.6, 72.8, 75.1, 84.0, 129.3, 131.0, 134.0, 147.0, 172.0. Anal. Calcd. for $C_{12}H_{14}O_6S$: C, 50.18; H, 5.27; S, 11.16. Found: C, 50.03; H, 5.11; S, 10.95.

(-)-(R)-3-Tosyloxy-5-methyl-2(5H)-furanone, 9.

A mixture of tosylate **8** (0.80 g, 2.79 mmol) and acetic anhydride (2 ml) in anhydrous pyridine (10 ml) was stirred at room temperature overnight. Then the solution was worked-up and purified as described above for tosylate **8**, to afford 0.71 mg (95% yield) of furanone **9**, m.p. 58-59° C (from chloroform-hexane), $[\alpha]_D$ -32.7° (c 2.62 in chloroform); ir (KBr): 3150, 2980, 2920, 1770, 1650, 1600, 1450, 1380, 1310, 1210, 1120 cm^{-1}; pmr ($CDCl_3$): 1.47 (d, J=6.7 Hz, 3H); 2.43 (s, 3H); 5.07 (dq, J=6.7 Hz, J'=1.8 Hz, 1H); 7.13 (d, J=1.8 Hz, 1H); 7.33 (d, J=8.26 Hz, 2H); 7.86 (d, J=8.26 Hz, 2H); cmr ($CDCl_3$): 19.1, 21.7, 75.2, 128.5, 130.0, 131.7, 136.4, 137.1, 146.5, 165.3. Anal. Calcd. for $C_{12}H_{12}O_5S$: C, 53.93; H, 4.49; S, 11.98. Found: C, 53.63; H, 4.54; S, 11.67.

(+)-(3S,5R)-3-Tosyloxy-5-methyldihydro-2(3H)-furanone, 10.

Furanone **9** (0.50 g, 1.86 mmol) in ethyl acetate (25 ml) and in the presence of 10% Pd/C (30 mg) was hydrogenated at 2 atm pressure and at room temperature for 16 hours. The mixture was filtered trough celite, the filter was washed with ethyl acetate (2x25 ml) and the solvent was removed at reduced pressure. The residue was flash-chromatographed on silica gel using dichloromethane as eluent, to give 0.48 g (95% yield) of tosylate **10** as an oil , $[\alpha]_D$ +16.7° (c 2.16 in chloroform); ir (film) 2930, 1788, 1600, 1366, 1179, 1126, 1071, 1051, 1001 cm^{-1}; pmr ($CDCl_3$): 1.44 (d, J=6.4 Hz, 3H); 2.1 (ddd, J=12.5 Hz, J'=11.7 Hz, J''=8.5 Hz, 1H); 2.85 (ddd, J=11.7 Hz, J'=10.8 Hz, J''=8.5 Hz, 1H); 4.50 (m, 1H); 5.13 (dd, J=10.8 Hz, J'=8.5 Hz, 1H); 7.35 (d, J=8.5 Hz, 2H); 7.89 (d, J=8.5 Hz, 2H); cmr ($CDCl_3$): 20.8, 21.6, 37.3, 73.5, 73.7, 128.1, 130.0, 132.8, 145.5, 170.0.

(+)-(3R,5R)-3-Azido-5-methyldihydro-2(3H)-furanone, 11.

A mixture of tosylate **10** (0.50 g, 1.85 mmol) and sodium azide (0.30 g, 4.6 mmol) in 15 ml of DMF was stirred at room temperature for 5 days. Then ethyl acetate (50 ml) was added and the solution was washed succesively with water and brine, and dried over magnesium sulfate. The solvent was evaporated at reduced pressure and the crude was flash-chromatographed, using 2:1 hexane-ethyl acetate as eluent, giving 0.24 g (94% yield) of a colorless oil, $[\alpha]_D$ +221.0° (c 3.48 in chloroform), that decomposes under distillation; ir (film) 2956, 2931, 2118, 1781, 1321, 1259, 1178, 955 cm^{-1}; 400 MHz pmr ($CDCl_3$) 1.35 (d, J=6.5 Hz, 3H); 2.06 (m, 1H); 2.18 (m, 1H); 4.30 (dd, J=6.0 Hz, J'=8.0 Hz, 1H); 4.70 (m, 1H); 100 MHz cmr ($CDCl_3$): 20.8, 35.4, 57.3, 75.5, 172.9.

(+)-(3R,5R)-2-Amino-5-methyldihydro-2(3H)-furanone, 4a.

Azide **11** (0.18 g, 1.30 mmol) in ethyl acetate (15 ml) and in the presence of 10% Pd/C (20 mg) was hydrogenated at atmospheric pressure and room temperature for three hours. Then the mixture was filtered trough celite and the filter was washed with ethyl acetate (3x25 ml). The solvent was removed at reduced pressure and the residue was dissolved in ethanol (3 ml) and stirred with 12 M HCl (2 ml) for 30 min. After evaporation of the solvents at 75º C/0.06 torr, the crude was crystallized from 4:1 ether-ethanol giving 175 mg (89% yield) of **4a** hydrochloride, m.p 164-167° C (dec) $[\alpha]_D$ +41.0° (c 4.3 in water). (Lit[7] m.p. 166-167.5° C; $[\alpha]_D$ -8.5° for the enantiomer of **4a**, obtained from the isolated natural product. See note in ref. 7); ir (KBr): 3000-2500, 1774, 1485, 1229, 1205, 1164, 1103 cm^{-1}; pmr (D_2O): 1.35 (d, J=6.3 Hz, 3H); 2.47 (m, 2H), 4.50 (t, J=9.6 Hz, 1H), 4.9 (m, 1H); cmr (D_2O): 22.3, 34.4, 50.5, 79.7, 176.6.

(-)-erythro-γ-Hydroxynorvaline, 4.

Hydrochloride **4a** (125 mg, 0.82 mmol) was passed through a Dowex 50Wx2 resin, using successively water and 0.3N NH_4OH as eluents, to afford amino acid **4** (82 mg, 88% yield); m.p. 192-194° C, $[\alpha]_D$ -35.2 (c 0.6 in water). (Lit[7] m.p. 192-193° C, $[\alpha]_D$ +25° (c 1.5 in water) for the synthetic enantiomer of **4**, and $[\alpha]_D$ +3.5° for the natural product. See note in ref. 7); ir (KBr): 3500-2500, 1632, 1588, 1474, 1412, 1351, 1126 cm^{-1}; pmr (D_2O) 1.04 (d, J=6.3 Hz, 3H); 1.59 (ddd, J=14.7 Hz, J'= 9.3 Hz, J''= 9.3 Hz, 1H); 1.9 (ddd, J=14.7 Hz, J'=3.9 Hz, J''=3.9 Hz, 1H); 3.6 (dd, J=9.3 Hz, J'=4.5 Hz, 1H); 3.87 (m, 1H); 100 MHz cmr (D_2O): 23.4, 39.2, 54.9, 67.4, 175.6

(-)-(3S,4R,5R)- and (+)-(3R,4R,5R)-3-Azido-4-hydroxy-5-methyldihydro-2(3H)-furanone, 12a and 12b.

(1) **From tosylate 8.** A mixture of tosylate **8** (0.39 g, 1.36 mmol) and sodium azide (0.13 g, 2.04 mmol) in anhydrous DMF (15 ml) was stirred for 5 days at room temperature. A g.c. control of the reaction mixture revealed a 7:3 mixture of azides **12a/12b**, and the absence of starting material. Then, ethyl acetate (50 ml) was added and the solution was washed with water (5x10 ml) and brine (10 ml), and dried over sodium sulfate. The solvents were removed at reduced pressure and the residue was flash-chromatographed on silica gel using 4:1 hexane ethyl acetate as eluent, to afford 133 mg of **12a** and 57 mg of **12b** (89% total yield), as colorless liquids that decomposed under heating.

(2) **From epoxy lactone 17.** To a stirred solution of **17** (0.22 g, 1.9 mmol) in 2 ml of anydrous DMF a mixture of trimethylsilyl azide (0.504 ml, 3.8 mmol) and anhydrous methanol (0.250 ml, 6.16 mmol) was added under argon atmosphere. The resultant mixture was stirred for 14 h at 60° C. Then, the reaction mixture was diluted with ethyl acetate (25 ml), washed with water (4x10 ml) and brine (10 ml), and dried over sodium sulfate. The solvents were removed at reduced pressure and the residue was flash-chromatographed on silica gel using 4:1 hexane-ethyl acetate as eluent, to give 147 mg of **12a** and 46 mg of **12b** (65% total yield).

Azide **12a**: $[\alpha]_D$ -111.8° (c 2.95 in chloroform); ir (film) 3600-3100, 2960, 2940, 2220, 2100, 1760, 1440, 1370, 1350, 1310, 1250, 1210, 1170, 1120, 1100, 1050 cm^{-1}; pmr ($CDCl_3$): 1.48 (d, J=6.2, 3H), 3.90 (t, J=J'=8.1 Hz, 1H); 4.29 (d, J=8.1 Hz, 1H); 4.31 (m, 1H); cmr ($CDCl_3$) 17.7, 64.8, 78.0, 78.8, 170.9. ms, m/e (%) 158 (M, 0.5), 157 (2.3), 75 (5.9), 71 (10.9), 70 (7.2), 59 (8.4), 58 (92.7), 57 (100), 56 (7.5), 55 (12.3).

Azide **12b**: $[\alpha]_D$ +97.2° (c 2.95 in chloroform); ir (film): 3650-3100, 2980-2900, 2110, 1770, 1400, 1380, 1360, 1170, 1100, 1060, 1020 cm^{-1}; pmr ($CDCl_3$): 1.40 (d, J=6.8 Hz, 3H); 4.13 (dd, J=5.1 Hz, J'= 1.8 Hz, 1H); 4.32 (d, J=5.1 Hz, 1H); 4.58 (dq, J=6.8 Hz, J'=1.8 Hz, 1H).

(-)-(R)-3-Azido-5-methyl-2(5H)-furanone, 13.

A mixture of azides **12a/12b** (0.24 g, 1.50 mmol), acetic anhydride (0.3 ml) and anhydrous pyridine (3 ml) was stirred for 20 hours. Then, water was added (40 ml) and the mixture was extracted with ethyl acetate (2x40 ml). The combined organic extracts were washed with 5% HCl and dried over sodium sulfate. The solvent was evaporated at reduced pressure and the residue was flash-chromatographed on silica gel using 7:3 hexane-ethyl acetate, to afford the unsaturated azide **13** (0.28 g, 85% yield), as a colorless oil that decomposed under heating. $[\alpha]_D$ -73.6° (c 1.63 in chloroform); ir (film) 2100, 1780, 1600 cm^{-1}; pmr ($CDCl_3$): 1.43 (d, J=6.6 Hz, 3H); 5.06 (dq, J=6.6 Hz, J'=1.3 Hz, 1H); 7.56 (d, J=1.3 Hz, 1H); cmr ($CDCl_3$): 19.2, 76.5, 129.0, 132.7, 167.4; ms, m/e (%) 140 (M+1, 6.3), 139 (M, 9.9), 68 (12.6), 67 (78.5), 66 (33.5), 54 (43.4), 52 (65.1), 43 (97.2), 41 (91.6), 40 (97.0).

(-)-threo-γ-Hydroxynorvaline, 3.

W2 Ra-Ni (150 mg) in 5 ml of ethanol was added to a solution of azide **13** (0.38 g, 2.76 mmol) in ethanol (10 ml), and the mixture was hydrogenated at atmospheric pressure and room temperature for 72 h. Then the mixture was filtered and the filter was washed exhaustively with ethanol . The solvent was removed in vacuo and the residue was dissolved in ethyl acetate, then vigorously stirred, and filtered through celite. The solvent was evaporated and the crude was poured into absolute ethanol (10 ml) containing conc HCl (4ml). After stirring the resultant solution for 30 min the solvent was removed at reduced pressure to give an oil that was passed through a Dowex 50Wx2 resin, using successively water and 0.3N NH_4OH as eluents to afford amino acid **3** (271 mg, 74% yield); m.p. 194-196° C (from acetone-water); $[\alpha]_D$-30.5 (c 0.75 in water). (Lit[7] m.p. 194-195° C; $[\alpha]_D$ -35.5° (c 0.5 in water); ir (KBr): 3400-2500, 1600, 1589, 1515, 1412, 1353 cm^{-1}; pmr (D_2O): 1.04 (d, J=6.5 Hz, 3H); 1.80 (m, 2H); 3.70 (m, 1H); 3.80 (m, 1H); 100 MHz cmr (D_2O): 23.6, 38.6, 54.1, 66.1, 175.3.

(+)-(3S,4R,5R)-3-Benzyloxycarbonylamino-4-hydroxy-5-methyldihydro-2(3H)-furanone, 19a.

Azide **12a** (0.17 g, 1.05 mmol) in 15 ml of ethyl acetate was hydrogenated in the presence of 10% Pd/C (20 mg), at atmospheric pressure for 2.5 hours at room temperature. The mixture was filtered through celite and the filter was washed with ethyl acetate (2x5 ml). The filtrate was concentrated to 20 ml volume and then saturated aqueous Na_2CO_3 (5 ml) and benzyl chloroformate (0.365 ml, 2.5 mmol) were added. The resultant mixture was stirred for 30 min at 0° C and for further 30 min at room temperature. Then, 10 ml of water was added, the phases were separated and the aqueous layer was extracted with ethyl acetate (2x10 ml). The combined organic layers were dried over sodium sulfate and the solvents were removed at reduced pressure. The reaction crude was flash-chromatographed on silica gel using mixtures of hexane-ethyl acetate as eluyent, to give carbamate **19a** (0.23 g, 875 yield); m.p. 144-146° C (from chloroform); $[\alpha]_D$ +56.4 (c 0.78 in chloroform) (Lit[16] 143-144° C, $[\alpha]_D$ -57° (c 0.78 in chloroform) for the enantiomer); ir (KBr) 3350, 3050, 2980-2920, 1770, 1680, 1550, 1450, 1380, 1250, 1220, 1060, 1030 cm^{-1}; pmr ($CDCl_3$): 1.50 (d, J=6.0 Hz, 3H), 3.99(t, J=J'=8.2 Hz, 1H); 4.16 (d, J=8.2 Hz, 1H); 4.37 (m, 1H); 5.14 (s, 2H), 5.62 (s, NH), 7.35 (s, 5H); cmr ($CDCl_3$): 18.2, 60.1, 67.9, 78.2, 79.8, 128.9, 129.0, 129.4, 137.8, 158.3, 174.1; ms, m/e (%) 265 (M, 0.5), 108 (5.6), 107 (2.2), 105 (2.8), 92 (6.5), 91 (100), 90 (5.6), 89 (7.4), 79 (3.8), 78 (2.7), 77 (6.4), 65 (21.8), 43 (26.4). Anal. Cald. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.67; H, 5.70; N, 5.27.

(-)-(3R,4R,5R)-3-Benzyloxycarbonylamino-4-hydroxy-5-methyldihydro-2(3H)-furanone, 19b.

Following the same procedure described above for the isomer **19a**, carbamate **19b** was obtained. m.p. 135-137° C (from chloroform), $[\alpha]_D$ -8.0° (c 0.69 in chloroform) (Lit[16] $[\alpha]_D$+7 (c 0.69 in chloroform) for the enantiomer); ir (KBr) 3600-3400, 3280, 3080, 2960, 2920, 2860, 1770, 1680, 1560, 1450, 1360, 1270, 1210, 1200, 1100, 1050, 1020 cm^{-1}; pmr ($CDCl_3$): 1.32 (d, J= 6.7 Hz, 3H); 4.30 (m, 1H); 4.45 (dq, J=6.7 Hz, J'=1.3 Hz, 1H); 4.62 (d, J=5.6 Hz, 1H); ms, m/e (%) 265 (M, 5.1), 108 (2.3), 91 (100), 77 (2.3), 65 (4.7).

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