Tetrahedron Vol. 46, No. 1, pp. 215-230, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

SYNTHETIC METHODS FOR THE PREPARATION OF BASIC D- AND L-PSEUDO-SUGARS. SYNTHESIS OF CARBOCYCLIC ANALOGUES OF *N*-ACETYL-MURAMYL-*L*-ALANYL-*D*-ISOGLUTAMINE (MDP)†

Derek H.R. Barton[a], S. Augy-Dorey[b], J. Camara[b], P. Dalko[b], J.M. Delaumény[b], S.D. Géro[b], B. Quiclet-Sire*[b] and P. Stütz[c].

[a]Department of Chemistry, Texas A&M University, College Station, Texas 77843, U.S.A.
[b]Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette Cedex, France.
[c]Sandoz Forschungsinstitut, Gesellschaft M.B.H., Brunnerstrasse 59, A-1230 Vienne, Austria.

(*Received in Canada* 11 *May* 1989)

ABSTRACT - Two exocyclic olefins **10** and **22**, readily elaborated from *D*-glucosamine, have been transformed by Ferrier rearrangement reaction into amino-cyclohexanones **11**, **12** and **23**, **24**. Reduction of ketone **11** with tri-t-butoxy-aluminium hydride followed by sequential acetylation and hydrogenolysis gave the acid **14** which was coupled with dipeptide **15** to provide **16**. Alkaline hydrolysis of the latter afforded **1**, a carbocyclic nor-analogue of MDP. The second target molecule **2** was prepared from an oxazolidine-pseudo-*D*-glucosamine **27**, obtained by treatment of amino-cyclohexanone **23** with methoxymethylenetriphenylphosphorane and mercuric acetate-sodium borohydride reagents, as key steps in the synthesis. On the other hand, hydroboration of the olefin **31** yielded pseudo-*L*-idosamine derivative **28**. Birch reduction of **27**, followed by sequential benzylidenation, etherification with (S)-α-chloropropionic acid and condensation of the resulted **36** with dipeptide **15**, gave **36**. Hydrogenolysis of the latter afforded the carbocyclic analogue **2** of MDP.

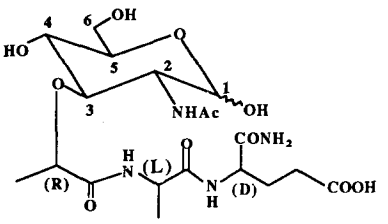
For some time now we have been interested[1] in the synthesis of *pseudo*-saccharides, where the ring oxygen of a normal sugar has been replaced by a methylene group. This nominally simple modification should give rise to isosteres with modified and interesting biological activity.[2]

The continued discovery of important classes of natural products like the fortimicins,[3] the validamycins,[4] the novel inhibitors of α-glycosidases such as acarbose[5] and oligostatine,[6] shares the value of this area of organic synthesis. It seemed to us that it would be important to replace the *D*-glucosamine present in immunostimulating compounds like *N*-acetyl-muramyl-*L*-alanyl-*D*-isoglutamine (MDP) by the corresponding *pseudo D*-glucosamine in the hope that the biological activity of MDP would be advantageously modified. At the same time the activity of *pseudo-D*-glucosamine itself deserved attention. The *pseudo-D*-glucosamine, like *D*-glucosamine, might inhibit the replication of certain viruses[7].

† Dedicated with respect to the memory of Professor Edgar Lederer.

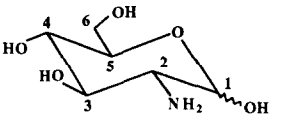
We describe in this paper the synthesis of the compound **1**, a *pseudo*-sugar nor-analogue of MDP. We also report on the synthesis of the *pseudo*-sugars **3** and **4** and on the conversion of the *pseudo*-D-glucosamine **3** into the desired carbocyclic analogue **2** of MDP.

There is little information in the literature on the synthesis of *pseudo-D*-glucosamine[1a,8,19] and of *pseudo-L*-idosamine. Since the pioneering work of H.O.L. Fischer[9] much effort has been expended on the conversion of carbohydrates into cyclohexane polyols. A major advance, however, was provided by the work of Ferrier.[10] The rearrangement reaction of Ferrier consists of the opening of a pyranose ring to give an aldehydo-ketone, cyclisation of which in an aldol-type reaction affords the desired polyhydroxycyclohexanone. We have used this reaction in the transformation of the exocyclic olefins **10** and **22** into the amino-cyclohexanone derivatives **11** and **23**. It is noteworthy that **10** possesses a lactoyl grouping at C_3.

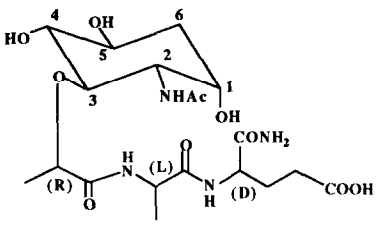


L-Ala D-isoGLn

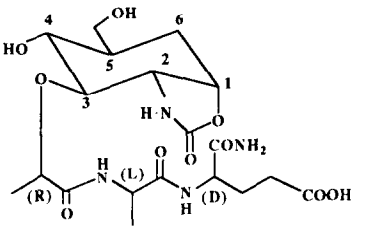
MDP



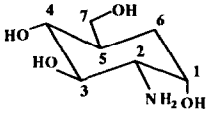
D- GLUCOSAMINE



1

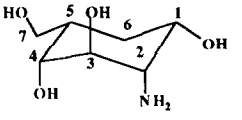


2



PSEUDO-D-GLUCOSAMINE

3



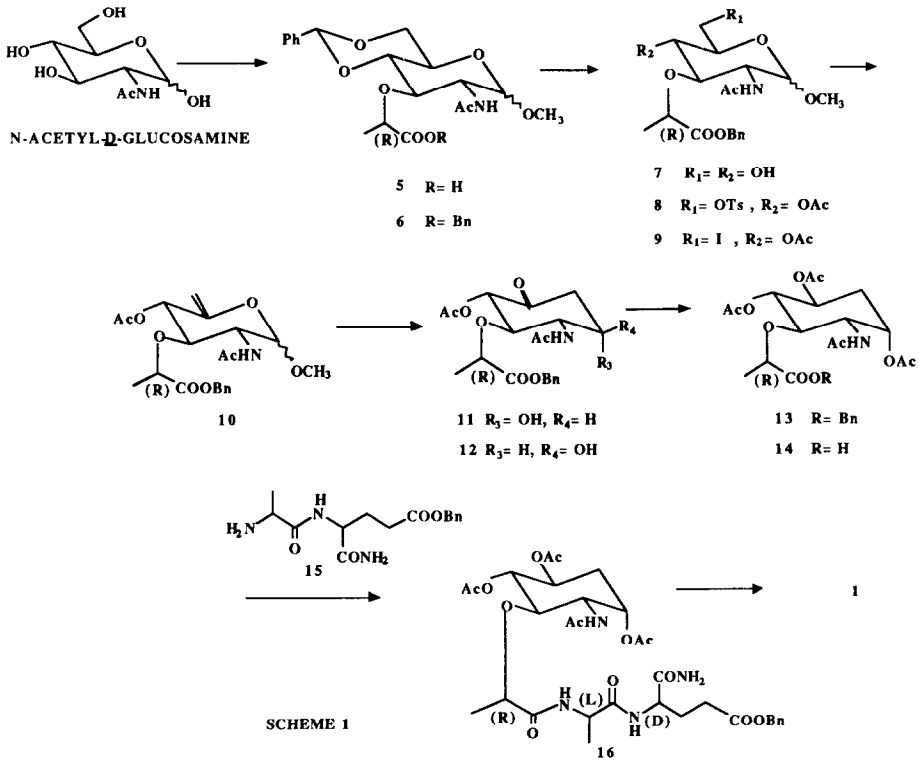
PSEUDO-L-IDOSAMINE

4

Synthesis of the Nor-analogue 1 of MDP

This synthesis started with methyl-4,6-*O*-benzylidene-muramic acid[11] **5**, readily available from *N*-acetylglucosamine. The acid **5** was esterified with benzyl bromide in presence of potassium carbonate in *N,N*-dimethylformamide (DMF) to give ester **6**. Acid catalysed hydrolysis afforded diol **7** which was selectively converted to the primary tosylate and then acetylated to give **8**. Treatment of the latter with potassium iodide in DMF afforded the crystalline iodide **9**. This was converted by reaction with silver fluoride in pyridine into the exocyclic olefin **10**. The overall yield from starting acid **5** was 34%.

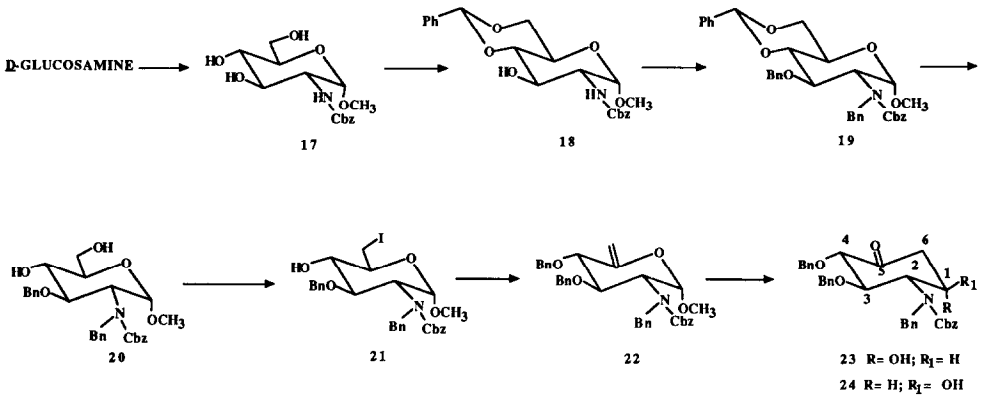
In the presence of a catalytic amount of mercuric sulfate in dioxan with aqueous sulfuric acid at 80°C, the olefin **10** was smoothly converted into ketone **11** and **12** with a good stereoselectivity (9:1 respectively). The ketone **11** was reduced by lithium tri-*t*-butoxyaluminium hydride in tetrahydrofuran to the equatorial alcohol, which on acetylation afforded the triacetate **13**. Hydrogenolysis of the latter in ethanol using palladium gave the acid **14** which was condensed with *L*-ala-*D*-isoglutamine benzyl ester[12] **15** using dicyclohexylcarbodiimide-*N*-hydroxysuccinimide to furnish **16**. Alkaline hydrolysis of **16** afforded the desired derivative **1**.



Synthesis of pseudo-*D*-glucosamine 3 and of pseudo-*L*-idosamine 4

The preferred intermediate **23** for **3** and **4** was easily prepared from *D*-glucosamine (Scheme 2). The known derivative **17** was prepared as already described.[13] Methyl 4,6 *O*-benzylidene-2-*N*-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside **18** was readily prepared by treatment of **17** with benzaldehyde-$ZnCl_2$. Reaction of **18** with benzyl bromide in presence of sodium hydride in DMF furnished the crystalline **19**. Hydrolysis of **19** in aqueous acetic acid afforded the diol **20** (84%). This was selectively converted to the iodide **21** (60%) using the method of Garegg[14] (triphenylphosphine-imidazole-iodine). Benzylation of **21** using sodium hydride and benzyl bromide in DMF gave the desired olefin **22** in good yield (80%). If this method is general it is superior to the method using the expensive silver fluoride (see above).

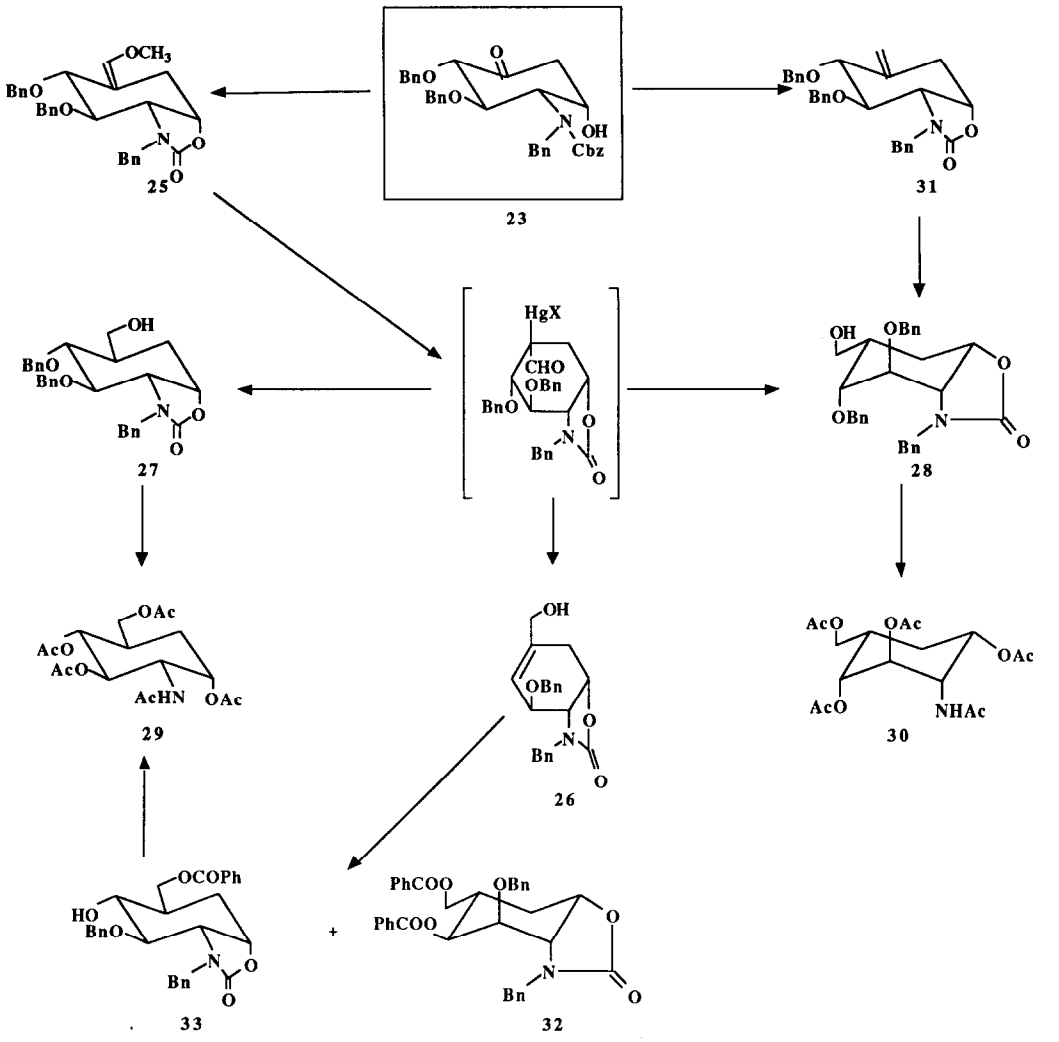
The conversion of **22** into **23** and **24** was carried out using two different catalyst systems. First, using palladium chloride,[15] the rearrangement afforded **23** and **24** (70%) in a ratio 3:2 respectively. A recent publication by Adam[16] has also disclosed the use of Pd^{II} for this type of reaction. Secondly, the use of mercuric sulfate afforded a mixture of **23** and **24** (75%) in a ratio of 85:15 respectively. Because of the selectivity of this reaction for the desired α-hydroxy isomer **23** we have used it in the sequel.



Scheme 2

To prepare the *pseudo*-sugars **3** and **4** we needed to homologate the ketone **23**. This was carried out in two steps (Scheme 3). The ketone **23** was reacted with methoxymethylene-triphenylphosphorane to furnish the olefin **25** (60%). In this derivative the oxazolidine ring between positions 1 and 2 was formed, a not unexpected transformation.[1a] This feature, with the five-membered ring fused rigidly to the six-membered, helps in promoting stereoselectivity.[17] Treatment of the vinyl ether **25** with mercuric nitrate in aqueous acetonitrile, followed by reduction with sodium borohydride, gave exclusively the allylic alcohol **26** (83%). On the other hand, when the reaction

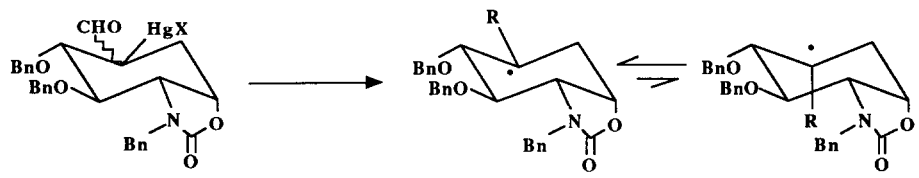
sequence was carried out using mercuric acetate in the same solvent a mixture of alcohols **27** and **28** was formed (65%) in a ratio of 4:1 respectively. By simple crystallisation the major isomer **27**, with the *D*-gluco configuration, could be isolated. Physico-chemical data established that the minor isomer was **28** with the *L*-ido configuration.



Scheme 3

The different behaviour of mercuric nitrate and of mercuric acetate suggests that the coordination of Hg^{2+} to the vinyl ether **25** does require in both cases mercury bonding. The mercury nitrate leaves at the same time as the adjacent protonated benzyloxy anion to furnish the allylic alcohol **26** or, more probably, its adehyde precursor. In constrast the mercuric acetate has the mercury still bound to acetate. Hence the tendency to ionic elimination is less and there is time for the formation of the mercury hydrogen bond and subsequent radical chemistry.[18]

The more hindered side of the intermediate is the α-face. However, after formation of the carbon radical this must have time to equilibrate (A ⇌ B) and so it must be the thermodynamic stability of A which is more important than the more hindered approach to the molecule by the long mercury-hydrogen bond. Be these considerations as they may, the alkaline hydrolysis of alcohols **27** and **28** followed by hydrogenolysis over paladised charcoal and peracetylation furnished the two penta-acetates **29** and **30** respectively.



A **B**

R= CHO, CH_2OH

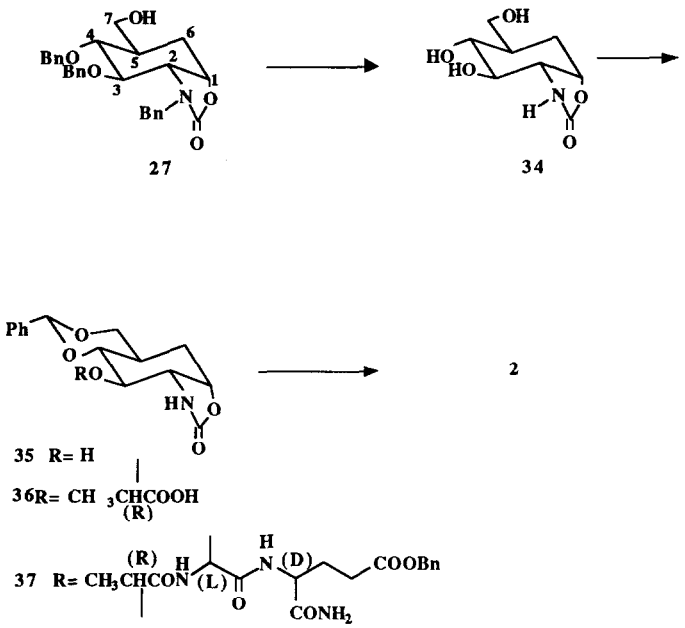
The *pseudo-L*-idosamine could also be obtained stereospecifically by hydroboration of the olefin **31**, formed by a traditional Wittig reaction of methylenetriphenylphosphorane on the ketone **23** accompanied by cyclisation across positions 1 and 2. Hydroboration of **31**, followed by the usual treatment with hydrogen peroxide, gave a single stereoisomer **28**. Clearly the hydroboration has taken place from the less hindered side of the molecule to furnish only the *L*-ido configuration.

As a complementary exercise the hydroboration of the allylic alcohol **26** was examined. After the same sequence of reactions, followed by benzoylation, a mixture of derivatives **32** and **33** was obtained in a ratio of 1:1. After basic treatment, hydrogenolysis and peracetylation **33** afforded the pentaacetate **29**, identical to the product previously obtained from **27**.

Synthesis of the Carbocyclic Analogue 2 of MDP

The intermediate **27** described above was used as starting material. Hydrogenolysis over palladium on charcoal gave only partial debenzylation. So **27** was treated with lithium in liquid ammonia (Birch reduction), using *t*-butanol as proton source, to give the triol **34**. Treatment with benzaldehyde-$ZnCl_2$ gave the derivative **35**. This was etherified by (*S*)-α-chloropropionic acid to give the derivative **36**, which was condensed with the dipeptide **15** as described already above, to

furnish **37** (78%). Hydrogenolysis of **37** over palladium on charcoal removed the benzyl and benzylidene groups to furnish the desired analogue **2** of MDP.



Scheme 4

Carbocyclic analogues of MDP **1** and **2** here described exhibit good immunostimulant properties and they are synergistic with LPS (lipopolysaccharides).

Experimental section

Microanalysis were performed by the Analytical Department, C.N.R.S., Gif-sur-Yvette. Melting point was determinated on a Reicher apparatus and are uncorrected. Optical rotations were measured with a polarimeter (Perkin-Elmer 141). ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometers: WP 80 (80 MHz), WP 200 (200 MHz, 50-33 MHz ^{13}C), WM 400 (400 MHz). Chromagel 60 A CC (230-400 mesh) SDS was used for column chromatography. HPLC chromatography was carried out on a silica gel Si 60 5μ and on a Alltech RSil column, NH_2, 10 μ. Chromatography was done by the flash column technique.

For better comprehension of NMR data of pseudo-sugars, the accepted nomenclature of carbohydrates was used.

Methyl 4,6-O-benzylidene-2-N-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside 18: Zinc chloride (70 g) in benzaldehyde (450 ml) was stirred for 30 mn. To this mixture, the triol **17** (70 g, 214 mmol) was added. After 24 h, the mixture was poured into ice-water-hexane (1:1) and the precipitate formed was filtered off, dried to yield **18** (66.8 g, 85%). Anal. Calcd. for C_{22} H_{25} N O_7: C, 63.60; H, 6.06; N, 3.37; O, 26.96. Found: C, 63.48; H, 6.13; N, 3.30. $[\alpha]_D^{20}$= +40° (c= 0.6 , DMF). Mp= 196-197°C. ^{13}C NMR δ (200 MHz, DMSO): 54.8 (CH_3); 56.5 (C_2); 62.4 (C_5); 65.5 (C_3); 67.3 ($CO_2\underline{CH_2}Ph$); 68.1 (C_6); 82.0 (C_4); 98.9 (C_1); 101.0 (C_7); 126.3-137.8 (Ph); 156.0 (CO).

Methyl 4,6 -O-benzylidene-3-O-benzyl-2-(N-benzyl-N-benzyloxycarbonyl-amino)-2-deoxy-α-D-glucopyranoside 19: Benzyl bromide (48 ml, 402 mmol) was added dropwise to a stirred suspension of sodium hydride (50% in oil) (19.3 g, 804 mmol) in N, N-dimethylformamide (200 ml). After cooling the mixture to 0°C, a solution of **18** (66.8 g, 161 mmol) in N, N-dimethylformamide (400ml) was added dropwise. After 3 h at room temperature, methanol was added and the mixture was diluted with ethyl acetate, neutralized with acetic acid and washed with water. The organic layer was dried ($MgSO_4$), filtered, evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-hexane,1:9) to afford **19** (72 g, 75%) which was crystallized from ethyl acetate-hexane. Anal. Calcd. for C_{36} H_{37} N O_7: C, 72.58; H, 6.26, N, 2.35. Found: C, 72.44; H, 6.29; N, 2.19. $[\alpha]_D^{20}$= + 77° (c= 0.66, $CHCl_3$). Mp= 103-104°C. ^{13}C NMR δ (200 MHz, $CDCl_3$): 47.1 ($\underline{CH_2}Ph$); 55.0 (OCH_3); 59.1 (C_2); 62.5 (C_5); 67.2 ($\underline{CH_2}Ph$); 69.1 (C_6); 73.1 (C_3); 73.3 ($\underline{CH_2}Ph$); 84.3 (C_4); 100.6 (C_1); 101.5 (C_7); 127.0-140.5 (Ph); 158.0 (CO).

Methyl 3-O-benzyl-2-(N-benzyl-N-benzyloxycarbonylamino)-2-deoxy-α-D-glucopyranoside 20: A suspension of **19** (70 g, 117mmol) in water acetic acid (900 ml, 1:2) was refluxed for 3 h. The mixture was coevaporated with water and the residue was dissolved in ethyl acetate, neutralized with a resin IR 45 OH^-. After filtration, the filtrate was evaporated under reduced pressure to give **20** quantitatively (59.2 g) which was used without futher purification.

Methyl 3-O-benzyl-2-(N-benzyl-N-benzyloxycarbonylamino)-2,6-dideoxy-6-iodo-α-D-glucopyranoside 21: To a solution of **20** (59.2 g, 116 mmol) in dry toluene (500 ml) were added under vigorous stirring triphenylphosphine (52 g, 198 mmol) and imidazole (19.1 g, 280 mmol). The mixture was heated at 60°C and then iodine (35.6 g, 140 mmol) was added in small portions. The mixture was heated at 80°C for 3 h cooled and then washed with water. The organic layers were combined, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on a silica gel column (ethyl acetate-hexane, 1:1) to yield the iodo-compound **21** (60%). Anal. Calcd. for C_{29} H_{32} I N O_6: C, 56.40; H, 5.22; N, 2.27. Found: C, 56.08; H, 5.35; N, 2.19. $[\alpha]_D^{20}$= + 60° (c= 1.05, $CHCl_3$). ^{13}C NMR δ (200 MHz, $CDCl_3$): 7.3 (C_6); 48.5 ($Ph\underline{CH_2}N$); 55.6 (OCH_3); 59.2 (C_2); 68.3 ($CO_2\underline{CH_2}Ph$); 71.4 (C_4); 73.7 ($\underline{CH_2}Ph$); 76.8, 77.7 (C_3, C_5); 100.5 (C_1); 126.6-140.4 (Ph); 158.2 (CO).

Methyl 3,4-di-O-benzyl-2-(N-benzyl-N-benzyloxycarbonylamino)-2-deoxy-α-D-xylo-hex-5-enopyranoside 22: Benzyl bromide (14.7 ml, 123.2 mmol) was added dropwise to a stirred suspension of sodium hydride (50% in oil) (11.8 g, 492 mmol) in N, N- dimethylformamide (100 ml). After cooling the mixture to 0°C, a solution of **21** (38 g, 61.6 mmol) in N, N-dimethylformamide (350ml) was added. After 5 h at room temperature, methanol was added and the mixture was diluted with ethyl acetate, neutralized with acetic acid and washed with water. The organic layer was dried ($MgSO_4$), filtered, evaporated to dryness. The residue was crystallized from ethyl acetate-hexane to afford **22** (28.3 g, 80%). Anal. Calcd. for C_{36} H_{37} N O_6: C, 74.59; H, 6.43. Found: C, 74.48; H, 6.52. $[\alpha]_D^{20}$= + 53° (c= 1.33, $CHCl_3$). Mp: 74-75°C. ^{1}H NMR δ (200 MHz, $CDCl_3$): 3.83 (s, 3H, OCH_3); 4.50 (m, 2H, H_2, H_3); 4.72 (m, 7H, 3 $\underline{CH_2}Ph$, H_1); 5.10 (m, 2H, H_6, $H_{6'}$); 6.90-7.50 (m, 20H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 47.1 ($N\underline{CH_2}Ph$); 54.8 (OCH_3); 58.6 (C_2); 67.5, 73.9, 74.2 ($\underline{CH_2}Ph$); 75.9 (C_3); 81.7 (C_4); 96.9 (C_6); 100.4 (C_1); 125.7-138.5 (Ph); 153.8 (C_5); 158.9 (CO).

2L-(2,4,5/3) 2,3-Di-O-benzyloxy-4-N-benzyl-4-N-benzyloxycarbonyl-amino-5-hydroxy-cyclohexanone 23:

Method A: A solution of alkene **22** (1 g, 1.73 mmol) and palladium (II) chloride (0.062 g, 0.35 mmol) in dioxane-aqueous H_2SO_4 5 mM (15 ml, 2:1) was heated at 80°C for 45 mn. The cooled mixture was filtered on celite and extracted with methylene chloride. The organic layer was washed with water, dried ($MgSO_4$), filtered and evaporated to dryness to give a residue which contained α-isomer **23** and β-isomer **24** in a ratio 6:4. The diastereoisomers were purified by flash chromatography (ethyl acetate-hexane, 3:7) to afford **23** (0.4 g) and **24** (0.27 g) (70%).

Method B: A solution of alkene **22** (28.3 g, 48.8 mmol) and mercuric (II) sulfate (0.383 g, 1.32 mmol) in dioxane-aqueous H_2SO_4 5 mM (525 ml, 2:1) was heated at 80°C for 3 h. The cooled mixture was extracted with methylene chloride. The organic layer was washed with water, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate-hexane, 3:7) to afford α-isomer **23** (18.2 g) and β-isomer **24** (2.6 g) (75%).

α isomer **23**: Anal. Calcd. for $C_{35}H_{35}NO_6$: C, 74.32; H, 6.24. Found: C, 74.41; H, 6.51. $[\alpha]_D^{20}$= -23° (c= 1.52, $CHCl_3$). ^1H NMR δ (200 MHz, $CDCl_3$): 2.3 (broad d, 1H, H_6); 2.5 (dd, 1H, H_6); 3.60 (m, 1H, OH); 4.0 -4.8 (m, H_2, H_1, H_4, H_3, CH_2Ph); 4.8-5.20 (m, CH_2Ph); 7.1-7.50 (m, 20H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 46.3 (C_6); 68.2 (CH_2Ph); 69.4 (C_1); 73.6, 75.4 (CH_2Ph); 77.1 (C_3); 88.1 (C_4); 127.5-138.4 (Ph); 158.2 (CO); 203.5 (C_5).

β isomer **24**: Anal. Calcd. for $C_{35}H_{35}NO_6$: C, 74.32; H, 6.24. Found: C, 74.47; H, 6.41. $[\alpha]_D^{20}$= -21° (c= 1.88, $CHCl_3$). ^1H NMR δ (200 MHz, $CDCl_3$): 2.45 (m, 1H, H_6); 2.7 (m,1H, $H_{6'}$); 4.0-4.4 (m, 3H, H_1, H_3, H_4); 4.4-5.2 (m, 8H, 4 CH_2Ph); 7.3 (m, 20H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 46.3 (C_6); 64.8 (C_1); 67.7, 73.4, 74.8 (CH_2Ph); 76.5 (C_3); 87.2 (C_4); 127-138 (Ph); 158.0 (CO); 203.0 (C_5).

1D-(1,2,4/3)-3,4-Di-O-benzyl-2-benzylamino-1,2-N,O-carbonyl-5-methoxy-methylene-1,3,4-cyclohexanetriol 25: To a solution of methoxymethylene-triphenylphosphonium chloride (17 g, 49.5 mmol) in 1,2-dimethoxyethane (200 ml) was added dropwise, at -70°C under argon, n-butyl lithium 1.1N (38.6 ml, 42.4 mmol). The mixture was allowed to warm to 0°C, a solution of cyclohexanone **23** (4 g, 7.07 mmol) in 1,2-dimethoxyethane (100 ml) was added dropwise. The mixture was stirred 45 mn and poured into ice-water saturated with ammonium chloride. After extraction with methylene chloride, the organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-hexane, 2:8) to yield **25** as an oil (2.1 g, 60%). Anal. Calcd. for $C_{30}H_{31}NO_5$: C, 74.20; H, 6.43; N, 2.88. Found: C, 73.96; H, 6.59; N, 2.78.$[\alpha]_D^{20}$= -12° (c= 1, $CHCl_3$). ^1H NMR δ (200 MHz, $CDCl_3$): 2.6 (dd, 1H, H_6, $J_{6,6'}$= 15 Hz, $J_{1,6}$= 6 Hz); 2.8 (dd, 1H, $H_{6'}$, $J_{1,6'}$= 7 Hz); 3.56 (dd, 1H, H_2, $J_{2,3}$= 8 Hz); 3.7 (s, 3H, OCH_3); 3.9 (m, 2H, H_3, H_4); 4.7 (m, 1H, H_1, $J_{1,2}$= 4 Hz); 5.0-4.1 (m, 6H, CH_2Ph); 6.2 (s, 1H, H_7); 7.4 (m, 15H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 23.9 (C_6); 46.8 (NCH_2Ph); 56.7 (C_2); 72.2 (C_1); 69.9, 72.7 (CH_2Ph); 78.0-78.1 (C_3, C_4); 106.5 (C_5); 148.7 (C_7); 158.3 (CO).

1D-(1,2,4/3)-3,4-Di-O-benzyl-3-benzylamino-1,2-N,O-carbonyl-5-methylene-1,3,4-cyclohexanetriol 31: To a solution of methylenetriphenyl-phosphonium bromide (3.62g, 10.1 mmol) in 1,2-dimethoxyethane (60 ml) was added dropwise, at -70°C under argon, n-butyl lithium 1N (8.45 ml, 8.45 mmol).The mixture was allowed to warm to 0°C and a solution of cyclohexanone **23** (0.956 g, 1.69 mmol) in 1,2-dimethoxyethane (40 ml) was added dropwise. The mixture was stirred 45 mn and poured into ice-water saturated with ammonium chloride. After extraction with methylene chloride, the organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-hexane, 3:7) to yield **31** which was crystallized from ether (0.5 g, 67%). Anal. Calcd. for $C_{29}H_{29}NO_4$: C, 76.46; H, 6.42, N, 3.07. Found: C, 76.15; H, 6.36; N, 3.18. $[\alpha]_D^{20}$= -49° (c= 1.6, $CHCl_3$). Mp= 87-88°C. ^1H NMR δ (200 MHz, $CDCl_3$): 2.6 (dd, 1H, H_6, $J_{6,6'}$= 15 Hz, $J_{1,6}$= 6 Hz); 2.8 (dd, 1H, $H_{6'}$, $J_{6',1}$= 5 Hz); 3.6 (t, 1H, H_2, $J_{2,3}$= 6 Hz); 3.9 (t, 1H, H_3, $J_{3,4}$= 6 Hz); 4.0 (d, 1H, H_4); 4.7 (m, 7H, 3 CH_2Ph, H_1, $J_{1,2}$=

6 Hz); 5.4 (d, 2H, H_7,$H_{7'}$); 7.4 (m, 15H, Ph).^{13}C NMR δ (200 MHz, $CDCl_3$): 33.1 (C_6); 46.4 (NCH_2Ph); 56.8 (C_2); 71.1, 73.1 (CH_2Ph); 73.4 (C_1); 80.5, 80.1 (C_3, C_4); 115.3 (C_7); 141.2 (C_5); 157.9 (CO).

1D-(1,2,4/2,5)-3,4-Di-O-benzyl-2-benzylamino-1,2-N,O-carbonyl-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 27: To a solution of vinylether **25** (3.8 g, 7.8 mmol) in acetonitrile (250 ml) was added dropwise at -5°C a solution of mercuric (II) acetate (2.74 g, 8.6 mmol) in water (50 ml). The mixture was stirred at 0°C for 4 h and potassium iodide (6.5 g, 39 mmol) in water (2 ml) was added. The mixture was diluted with methylene chloride and the organic phase was washed with water, dried ($MgSO_4$) , filtered and evaporated to dryness. The residue was dissolved in tetrahydrofuran (150 ml) and sodium borohydride (1.16 g, 31.3 mmol) was added in small portions. The mixture was stirred at 0°C overnight and filtered on celite. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with aqueous citric acid, water, dried ($MgSO_4$) , filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyle acetate-hexane,6:4) to afford a mixture of two alcohols **27** and **28** (2.4 g, 65%), (D-gluco and L-ido, 85:15). The alcohol 27 (D-gluco) was crystallized from the mixture from ethyl acetate-hexane.

D-gluco isomer **27:** Anal. Calcd. for C_{29} H_{31} N O_5: C, 73.55; H, 6.68, N, 2.93. Found: C, 73.40; H, 6.68; N, 2.84. $[\alpha]_D^{20}$= +10° (c= 1.0, $CHCl_3$). Mp= 95-96°C. ^{1}H NMR δ (400 MHz, $CDCl_3$): 1.7 (m, 1H, H_6); 1.9 (m, 1H, $H_{6'}$); 2.0 (m , 1H, H_5, $J_{5,7}$= 4Hz, $J_{7,5'}$= 3Hz); 3.5 (dd, 1H, H_4, $J_{4,5}$= 8Hz); 3.6 (dd, 1H, H_7, $J_{7,7'}$= 11Hz); 3.65 (dd, 1H, H_2, $J_{2,3}$= 6Hz); 3.75 (dd, 1H, $H_{7'}$); 3.77 (t, 1H, H_3, $J_{3,4}$= 6Hz); 4.6 (m, 1H, H_1, $J_{1,2}$= 4Hz); 4.6-4.9 (m, 6H, 3 CH_2Ph); 7.2 (m, 15H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 27.1 (C_6); 37.3 (C_5); 46.5 (NCH_2Ph); 56.3 (C_2); 64.0 (C_7); 73.0 (C_1); 73.1 (CH_2Ph); 78.3, 78.9 (C_3, C_4); 158.2 (CO).

L-ido isomer **28:** Anal. Calcd. for C_{29} H_{31} N O_5: C, 73.55; H, 6.68, N, 2.93. Found: C, 73.42; H, 6.72, N, 2.69. $[\alpha]_D^{20}$= -2.5° (c= 1.0, $CHCl_3$). ^{1}H NMR δ (400 MHz, $CDCl_3$): 1.8 (m, 2H, H_6, $H_{6'}$, $J_{6,6'}$= 13Hz, $J_{1,6}$= 6Hz); 2.05 (m, 1H, H_5, $J_{5,6'}$= 10Hz); 3.5 (dd, 1H, H_7, $J_{7,7'}$= 11Hz, $J_{7,5}$= 5Hz); 3.65 (m, 2H, H_2, $H_{7'}$, $J_{2,3}$= 3.5Hz); 3.7 (t, 1H, H_4, $J_{4,5}$= 3.5Hz); 3.75 (t, 1H, H_3, $J_{3,4}$= 3.5Hz); 3.8, 4.85 (2d, 2H, NCH_2Ph); 4.30 (q, 2H, CH_2Ph); 4.47 (q, 2H, CH_2Ph); 4.57 (m, 1H, H_1, $J_{1,2}$= 6Hz); 7.2 (m, 15H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 25.3 (C_6); 35.6 (C_5); 46.5 (NCH_2Ph); 56.8 (C_2); 63.1 (C_7); 72.8, 72.5 (C_1, C_3); 73.2 (CH_2Ph); 75.4 (C_4); 158.2 (CO).

1D-(1,2,4,5/3)-3,4-Di-O-benzyl-2-benzylamino-1,2-N,O-carbonyl-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 28: To a solution of **31** (0.82 g, 1.8 mmol) in tetrahydrofuran (5 ml) was added dropwise at O°C under argon a solution of diborane in tetrahydrofuran (1M, 10 ml). The mixture was stirred overnight at room temperature. The solution was treated overnight with water (2 ml), sodium hydroxide 3N (2 ml) and hydrogen peroxide 33% (2 ml). After extraction with methylene chloride, the combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-hexane, 6:4) to yield **28** (0.5g, 60%) identical to the compound obtained by oxy-mercuration.

1D-(1,2/3)-3-O-Benzyl-2-benzylamino-1,2-N,O-carbonyl-5-C-hydroxy-methyl-cyclohex-4-en-1,3-diol 26: To a solution of **25** (1 g, 2 mmol) in acetonitrile (80 ml) was added dropwise at -5°C a solution of mercuric (II) nitrate (0.6 g, 2.2 mmol) in water (16 ml). The mixture was stirred at 0°C for 4 h and potassium iodide (1.7 g, mmol) in water (2 ml) was added. The mixture was diluted with methylene chloride and the organic phase was washed with water, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was dissolved in tetrahydrofuran (150 ml) and sodium borohydride (0.23 g, 6 mmol) was added in small portions. The mixture was stirred at 0°C overnight and filtered on celite. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with aqueous citric acid, water, dried ($MgSO_4$) , filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate-hexane, 3:7) to afford the alcohol **26** (0.7 g, 93%) which was crystallized from ethyl acetate-hexane. Anal. Calcd. for C_{22} H_{23} N O_4: C, 72.27; H, 6.34; N, 3.83. Found: C, 71.86; H, 6.39; N, 3.84. $[\alpha]_D^{20}$= +61° (c= 1.15,

$CHCl_3$). Mp= 86-87°C. ^1H NMR δ (200 MHz, $CDCl_3$): 2.3 (dd, 1H, H_6, $J_{6,6'}$= 15Hz, $J_{6,1}$= 4Hz); 2.6 (dd, 1H, $H_{6'}$, $J_{6',1}$= 4.5Hz); 3.9 (dd, 1H, H_2, $J_{2,3}$= 3Hz); 4.0 (t, 1H, H_3, $J_{3,4}$= 4Hz); 4.1 (m, 2H, H_7, $H_{7'}$); 4.8-4.1 (m, 4H, $\underline{CH_2}Ph$); 4.9 (m, 1H, H_1, $J_{1,2}$= 9Hz); 6.0 (d, 1H, H_4); 7.4 (m, 10H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 28.7 (C_6); 46.9 ($N\underline{CH_2}Ph$); 58.3 (C_2); 65.6 (C_7); 70.7 ($\underline{CH_2}Ph$); 71.0 (C_3); 72.0 (C_1); 120.5 (C_4); 142.1 (C_5); 158.3 (CO).

1D-(1,2,5/3,4)-4,7-Di-O-benzoyl-3-O-benzyl-2-benzylamino-1,2-N,O-carbonyl-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 32 and 1D-(1,2,4/3,5)-7-O-Benzoyl-3-O-benzyl2-benzyl-amino-1,2-N,O-carbonyl-5-C-hydroxy-methyl-1,3,4-cyclohexanetriol 33: To a solution of **26** (3 g,8.2 mmol) in tetrahydrofuran (25 ml) was added dropwise at O°C under argon a solution of diborane in tetrahydrofuran (1M, 15 ml). The mixture was stirred overnight at room temperature. The solution was treated with water (3 ml), sodium hydroxide 3N (3 ml) and hydrogen peroxide 33% (3 ml). After extraction with methylene chloride, the organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was treated with pyridine (20 ml) and benzoyl chloride (3.7 ml). The mixture was poured into ice-water and extracted with ethyl acetate. The organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified on a silica gel column (ethyl acetate hexane, 6:4) to yield the alcohol **33** (1.6 g) which was crystallized from ethyl acetate-hexane and dibenzoate **32** (1.55 g).

Alcohol **33**: Anal. Calcd. for C_{29} H_{29} N O_6: C, 71.44; H, 5.99; N, 2.87 Found: C, 71.68; H, 6.11; N, 2.87. $[\alpha]_D^{20}$= +28° (c= 1, $CHCl_3$). Mp= 145-147°C. ^1H NMR δ (400 MHz, $CDCl_3$): 1.8 (td, 1H, H_6, $J_{6,6'}$= 14Hz, $J_{5,6}$= 12Hz, $J_{1,6}$= 4Hz); 2.18 (m, 1H, H_5); 2.33 (dt, 1H, $H_{6'}$, $J_{6',5}$= 3Hz, $J_{6',1}$= 3Hz); 3.33 (s, 1H, OH); 3.38 (m, 2H, H_2, H_4); 3.75 (t, 1H, H_3); 4.2, 4.73, 4.98, 5.13 (4d, 4H, 2 $\underline{CH_2}Ph$); 3.75 (t, 1H, H_3, $J_{3,2}$=$J_{3,4}$= 8Hz); 4.31 (dd, 1H, H_7, $J_{7,7'}$= 12Hz, $J_{7,5}$= 3Hz); 4.63 (m, 1H, H_1); 4.95 (dd, 1H, $H_{7'}$, $J_{7',5}$= 4Hz); 7.21-8.13 (m, 15H, Ph).^{13}C NMR δ (200 MHz, $CDCl_3$): 27.8 (C_6); 36.9 (C_5); 46.6 ($N\underline{CH_2}Ph$); 58.1 (C_2); 65.1 (C_7); 72.1 (C_1); 73.9 (C_4); 74.1 ($\underline{CH_2}Ph$); 83.7 (C_3); 138-127.8 (Ph); 158.1, 167.1 (CO).

Compound **32**: Anal. Calcd. for C_{36} H_{33} N O_7: C, 73.1; H, 5.62; N, 2.37. Found: C, 72.95; H, 5.73; N, 2.31. $[\alpha]_D^{20}$= -46° (c= 1.5, $CHCl_3$). ^1H NMR δ (400 MHz, $CDCl_3$): 1.93 (dt, 1H, H_6, $J_{1,6}$= $J_{5,6}$= 8Hz, $J_{6,6'}$= 14Hz); 2.4 (dt, 1H, $H_{6'}$, $J_{1,6'}$= $J_{5,6'}$= 6Hz); 2.75 (m, 1H, H_5, $J_{4,5}$= 8Hz); 3.81 (dd, 1H, H_2, $J_{1,2}$= 8Hz, $J_{2,3}$= 5Hz); 4.1 (m, 1H, H_3); 4.2-4.3 (2d, 2H, $\underline{CH_2}Ph$); 4.4 (m, 4H, H_7, $H_{7'}$, $\underline{CH_2}Ph$); 4.76 (m, 1H, $J_{1,2}$=8Hz); 4.88 (d, 1H, $\underline{CH_2}Ph$); 5.38 (d, 1H, H_4); 7-8.1 (m, 20H,Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 27.8 (C_6); 33.7 (C_5); 46.8 ($N\underline{CH_2}Ph$); 56.5 (C_2); 65.8, 74.1 ($\underline{CH_2}Ph$); 71.8 (C_1); 72.4 (C_4); 78.2 (C_3); 127.9-137.7 (Ph); 166.3, 165.7, 157.8 (CO).

1D-(1,2,4/3,5)-2-acetamido-1,3,4,7-tetra-O-acetyl-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 29 (pseudo-D-glucosamine pentaacetate): A solution of **27** (0.25 g, 0.52 mmol) or **33** (0.6 g, 1.01 mmol) in ethanolic-sodium hydroxide solution 10% (1:1) was refluxed under argon overnight. The mixture was extracted with ethyl acetate.The combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was dissolved in ethanol and hydrogenolysed (2 bars) on palladium on charcoal 10% for 2 days. The solution was filtered on celite and concentred under reduced pressure. The residue was treated with acetic anhydride in pyridine to yield **29** (0.12 g, 60% overall yield from **27** or 66% overall yield from **33**) which was crystallized from ethyl acetate-hexane. Anal. Calcd. for C_{17} H_{25} N O_9: C, 52.70; H, 6.50.N, 3.61. Found: C, 52.40; H, 6.33; N, 3.66. $[\alpha]_D^{20}$= +68° (c= 0.7, $CHCl_3$). Mp= 74-75°C. ^1H NMR δ (400 MHz, $CDCl_3$): 1.25 (m, 1H, H_6); 1.75 (m, 1H, $H_{6'}$); 1.95 (s, 3H, $\underline{CH_3}CONH$); 2.2-2.0 (m, 1H, H_5, 4s, 12H, 4 $\underline{CH_3}CO$); 3.9 (dd, 1H, H_7); 4.2 (dd, 1H, $H_{7'}$); 4.3 (td, 1H, H_2, $J_{2,3}$= 8.5Hz, $J_{2,NH}$= 8Hz); 5.15 (m, 2H, H_3, H_4, $J_{3,4}$= 9Hz, $J_{4,5}$= 9Hz; 5.25 (m, 1H, H_1, $J_{1,2}$= 2Hz); 5.85 (d, 1H, NH). ^{13}C NMR δ (200 MHz, $CDCl_3$): 29.5 (C_6); 35.2 (C_5); 52.5 (C_2); 63.1 (C_7). 71.5, 70.9 (C_3, C_4); 72.6 (C_1).

1D-(1,2,4,5/3)-2-Acetamido-1,3,4,7-tetra-O-acetyl-5-C-hydroxymethyl-1,3,4-cyclo-hexanetriol 30 (pseudo-L-idosamine pentaacetate): A solution of alcohol **28** (0.245g, 0.51 mmol) in ethanol-sodium hydroxide 10% (1:1) was refluxed under argon overnight.

The mixture was extracted with ethyl acetate.The combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was dissolved in ethanol and hydrogenolysed (2 bars) on palladium on charcoal (10%) for 2 days. The solution was filtered on celite and concentred under reduced pressure. The residue was treated with acetic anhydride in pyridine to yield **30** (0.105g, 60% overall yield from **28**). Anal. Calcd. for C_{17} H_{25} N O_9: C, 52.70; H, 6.50; N, 3.61. Found: C, 53.00; H, 6.84; N, 3.33. $[\alpha]_D^{20}$= +19.5° (c= 0.9, $CHCl_3$). ^{13}C NMR δ (200 MHz, $CDCl_3$): 26.0 (C_6); 35.0 (C_5); 51.0 (C_2); 63.5 (C_7); 69.4, 70.4 (C_3, C_4); 71.4 (C_1).

Methyl 2-Acetamido-4,6-O-benzylidene-3-O-[(R)-1'-benzylcarboxyethyl]-2-deoxy-α,β-D-glucopyranoside 6: Benzyl bromide (20.4 g, 119.4 mmol) was added at 0°C to a solution containing acid **5** (31.4 g, 79.5 mmol) and potassium carbonate (13.2 g, 95.7 mmol). The mixture was stirring at room temperature overnight. After evaporation to dryness, the residue was washed with water and hexane to yield **6** (ratio α:β, 9:1) (32.4 g, 84%) which was crystallized from methylene chloride-hexane. Anal. Calcd. for C_{26} H_{31} N O_8: C, 64.33; H, 6.39. Found: C, 64.28; H, 6.18. ^1H NMR δ (80 MHz, $CDCl_3$): 1.40 (d, 3H, $\underline{CH_3}CH$); 2.00 (s, 3H, $NCOCH_3$); 3.35 (s, 3H, OCH_3); 3.75 (m, 5H, H_2, H_3, H_4, H_6, $H_{6'}$); 4.25 (m, 1H, H_5); 4.55 (q, 1H, $CH_3\underline{CH}$); 5.15 (m, 3H, H_1, $\underline{CH_2}Ph$); 5.50 (s, 1H, H_7); 7.40 (m, 5H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 18.8 ($CH\underline{CH_3}$); 23.1 ($NHCO\underline{CH_3}$); 54.5 (C_2); 55.5 (OCH_3); 62.8 (C_5); 67.1 ($\underline{CH_2}Ph$); 69.2 (C_6); 74.9 (C_3); 75.4 ($\underline{CH}CH_3$); 83.6 (C_4); 98.7 (C_1); 101.5 (C_7); 120.0-137.4 (Ph); 170.9 ($\underline{CO_2}CH_2Ph$); 174.9 ($CH_3\underline{CO}N$).

Methyl 2-Acetamido-3-O-[(R)-1'-benzylcarboxyethyl]-2-deoxy-α,β–D-glucopyranoside 7: A suspension of **6** (30 g, 61.9 mmol) in water-acetic acid (450 ml, 1:2) was refluxed for 1 h. The mixture was coevaporated with water and the residue was crystallized from methanol-water to afford **7** (ratio α:β, 9:1) (17.8 g, 73%). Anal. Calcd. for C_{19} H_{27} N O_8: C, 57.43; H, 6.80, N, 3.52. Found: C, 57.14; H, 6.97; N 3.57. ^1H NMR δ (80 MHz, $CDCl_3$): 1.40 (d, 3H, $\underline{CH_3}CH$); 1.98 (s, 3H, $NCO\underline{CH_3}$); 3.45 (s, 3H, OCH_3); 3.95 (m, 6H, H_2, H_3, H_4, H_5, H_6, $H_{6'}$); 4.35 (q, 1H, $CH_3\underline{CH}$); 4.68 (s, 1H, H_1); 5.17 (s, 2H, $\underline{CH_2}Ph$); 7.35 (s, 5H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 19.1 ($CH\underline{CH_3}$); 23.4 ($NCO\underline{CH_3}$); 55.0 (C_2); 56.8 ($O\underline{CH_3}$); 62.2 (C_6); 66.9 ($\underline{CH_2}Ph$); 71.8 (C_5); 74.7 (C_4); 75.7 ($\underline{CH}CH_3$); 80.5 (C_3); 102.9 (C_1); 172.1 ($\underline{CO_2}CH_2Ph$); 175.0 ($\underline{CO}N$).

Methyl 2-Acetamido-4-O-acetyl-3-O-[(R)-1'-benzylcarboxyethyl]-2-deoxy-6-O-tosyl-α,β-D-glucopyranoside 8: Tosyl chloride (15 g, 137 mmol) was added at 0°C to a solution of **7** (12.3 g, 31 mmol) in dry pyridine (200 ml). The mixture was stirred at room temperature overnight and then to the cooled mixture acetic anhydride (8 ml, 78.8 mmol) and a catalytic amount of 4-dimethylaminopyridine were added. After 18 h, the mixture was poured into ice-water and extracted with ethyl acetate. After purification on a silica gel column (ethyl acetate-hexane, 3:1), the compound **8** (ratio α:β, 9:1) (12.4 g, 73%) was crystallized from ethyl acetate-hexane. Anal. Calcd. for C_{25} H_{43} N O_{10} S: C, 54.63; H, 7.88. Found: C, 54.58; H, 7.91. ^1H NMR δ (80 MHz, $CDCl_3$): 1.40 (d, 3H, $\underline{CH_3}Ph$); 2.00 (s, 3H, $NCO\underline{CH_3}$); 2.15 (s, 3H, $OCO\underline{CH_3}$); 2.45 (s, 3H, $\underline{CH_3}CH$); 3.35 (s, 3H, OCH_3); 3.85 (m, 3H, H_5, H_6, $H_{6'}$); 4.10 (m, 2H, H_2, H_3); 4.35 (q, 1H, $CH_3\underline{CH}$); 5.00 (t, 1H, H_4); 5.25 (m, 3H, $\underline{CH_2}Ph$, H_1); 7.45 (s, 5H, Ph); 7.90 (m, 4H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 18.6 ($CH\underline{CH_3}$); 20.6 ($\underline{CH_3}Ph$); 21.4 ($OCO\underline{CH_3}$); 22.9 ($NCO\underline{CH_3}$); 53.2 (C_2); 55.4 (OCH_3); 67.3, 67.7 ($\underline{CH_2}Ph$, C_5); 68.5 (C_6); 72.5 (C_3); 75.3, 75.5 (CH_3CH, C_4); 97.5 (C_1); 127.7-145 (Ph); 169.3 ($COCH_3$); 171.0 ($\underline{CO_2}CH_2Ph$); 174.3 ($\underline{CO}N$).

Methyl 2-Acetamido-4-O-acetyl-3-O-[(R)-1'-benzylcarboxyethyl]-2,6-dideoxy-6-iodo-α,β-D-glucopyranoside 9: Potassium iodide (13 g, 78.3 mmol) was added to a solution of **8** (12.4 g, 22.6 mmol) in N, N-dimethylformamide (50 ml). The mixture was heated at 100°C for 1 h and then poured into ice-water. The precipitate formed was filtered off to give the iodo-compound **9** (ratio α:β, 9:1) (11.3 g, 91%) which was crystallized from ethyl acetate. Anal. Calcd. for C_{21} H_{28} I N O_8: C, 45.90; H, 4.92. Found: C, 45.81; H, 4.99. ^1H NMR δ (80 MHz, $CDCl_3$): 1.35 (d, 3H, $\underline{CH_3}CH$) 2.00 (s, 3H, $NCO\underline{CH_3}$); 2.15 (s, 3H, $CO\underline{CH_3}$); 3.20 (m, 2H, H_6, $H_{6'}$); 3.50 (s, 3H,

OCH_3); 3.75 (td, 1H, H_2); 3.90 (m, 2H, H_3, H_5); 4.35 (q, 1H, $CH_3\underline{CH}$); 4.97 (t, 1H, H_4); 5.26 (q+m, 3H, $\underline{CH_2}Ph$, H_1); 7.50 (s, 5H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 3.9 (C_6); 18.9 ($CH\underline{CH_3}$); 21.1 ($OCO\underline{CH_3}$); 23.2 ($NCO\underline{CH_3}$); 54.4 (C_2); 55.9 (OCH_3); 67.5 ($\underline{CH_2}Ph$); 70.1 (C_5); 75.6, 75.7, 76.2 ($CH_3\underline{CH}$, C_3, C_4); 97.9 (C_1); 128.4 -135 (Ph); 169.8 ($\underline{CO}CH_3$); 171.0 ($\underline{CO_2}CH_2Ph$); 174.5 ($N\underline{CO}CH_3$).

Methyl 2-Acetamido-4-O-acetyl-3-O-[(R)-1'-benzylcarboxyethyl]-2-deoxy-α,β-D-xylo-hex-5-enopyranoside 10: The iodo-compound **9** (12.4 g, 22.6 mmol) was dissolved in dry pyridine (150 ml) and treated with silver fluoride (7 g, 55.1 mmol) at room temperature overnight. The pyridine was evaporated and the residue was purified on a silica gel column (ethyl acetate) to yield **10** (ratio α:β, 9:1) (7.9 g, 83%).Anal. Calcd. for C_{21} H_{27} N O_8: C, 59.84; H, 6.45. Found: C, 59.72; H, 6.50. ^1H NMR δ (200 MHz, $CDCl_3$):1.40 (d, 3H, $\underline{CH_3}CH$); 2.00 (s, 3H, $NCO\underline{CH_3}$); 2.20 (s, 3H, $OCO\underline{CH_3}$); 3.40 (s, 3H, OCH_3); 3.86 (dd, 1H, H_3); 4.06 (td, 1H, H_2); 4.46 (q+s, 2H, $CH_3\underline{CH}$, H_6); 4.73 (s, 1H, $H_{6'}$); 5.26 (q, 2H $\underline{CH_2}Ph$); 5.33 (d, 1H, H_1); 5.46 (d, 1H, H_4); 7.4 (s, 5H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 18.7 ($\underline{CH_3}CH$); 20.9 ($OCO\underline{CH_3}$); 23.3 ($NCO\underline{CH_3}$); 56.1, 56.3 (C_2, OCH_3); 71.9 (C_3); 75.3 ($\underline{CH}CH_3$); 77.8 (C_4); 94.5 (C_6); 102.6 (C_1); 128.8 -135.2 (Ph); 152.4 (C_5); 169.1 ($\underline{CO}CH_3$); 171.0 ($\underline{CO}CH_2Ph$); 173.5 ($\underline{CO}N$).

2L-(2,4,5/3)-4-Acetamido-2-O-acetyl-3-O-[(R)-1'-benzylcarboxyethyl]-5-hydroxy-cyclohexanone 11: A solution of alkene **10** (0.9 g, 2.21 mmol) and mercuric (II) sulfate (0.015 g) in dioxane-aqueous H_2SO_4 5 mM (35 ml, 2:1) was heated at 80°C for 2 h. The cooled mixture was extracted with methylene chloride. The organic layer was washed with water, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate) to afford **11** (0.450 g, 52%). Anal. Calcd. for C_{20} H_{25} N O_8: C, 58.97; H, 6.14; N, 3.44. Found: C, 58.82; H, 6.13; N, 3.52. $[\alpha]_D^{20}$= +21° (c= 0.7, CH_2Cl_2). Mp= 168°C. ^1H NMR δ (200 MHz, $CDCl_3$): 1.4 (d, 3H, $\underline{CH_3}CH$); 2.10 (s, 3H, $NCO\underline{CH_3}$); 2.2 (s, 3H, $OCO\underline{CH_3}$); 2.70 (m, 3H, H_6, $H_{6'}$, OH); 4.05 (m, 2H, H_2, H_4); 4.55 (q, 1H, $\underline{CH}CH_3$); 4.80 (m, 1H, H_1); 5.35 (m, 3H, $\underline{CH_2}Ph$, H_3); 7.45 (m, 5H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 18.7 ($\underline{CH_3}CH$); 20.5 ($OCO\underline{CH_3}$); 23.2 ($NCO\underline{CH_3}$); 44.4 (C_6); 56.3 (C_2); 65.6 (C_1); 67.4 ($\underline{CH_2}Ph$); 75.5, 76.3 ($\underline{CH}CH_3$, C_3); 81.3 (C_4); 128-128.7 (Ph); 169.1 ($\underline{CO}CH_3$); 171.8 ($\underline{CO_2}CH_2Ph$); 174.8 ($N\underline{CO}CH_3$); 198.9 (C_5).

1D-(1,2,4/3,5)-2-Acetamido-1,4,5-tri-O-acetyl-3-O-[(R)-1'-benzylcarboxy-ethyl]-1,3,4,5-cyclohexanetetrol 13: To a solution of **11** (0.850 g, 2.08 mmol) in dry tetrahydrofuran (25 ml) was added at 0°C under argon lithium aluminium-tri-tert-butoxyhydride (1.06 g, 4.18 mmol). The mixture was stirred at 0°C for 40 mn and then neutralized with acetic acid and evaporated to dryness. The residue was dissolved in methylene chloride (20 ml) and treated with acetic anhydride (2 ml), triethylamine (1 ml) and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at room temperature overnight and washed with water. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness to afford **13** as an oil (0.882 g, 86%) which was purified on a silica gel column (ethyl acetate-hexane, 8:2). Anal. Calcd. for C_{24} H_{31} N O_{10}: C, 58.42; H, 6.29; N, 2.84. Found: C, 58.30; H, 6.40; N, 2.62. {$[\alpha]_D^{20}$= +42° (c= 1.14, CH_2Cl_2). ^1H NMR δ (400 MHz, $CDCl_3$): 1.4 (d, 3H, $\underline{CH_3}CH$); 1.80 (t, 1H, H_6, $J_{6,6'}$= 14Hz, $J_{6,1}$= 2Hz); 2.00 (2s, 6H, $NHCO\underline{CH_3}$, $OCO\underline{CH_3}$); 2.10 (2s, 6H, $OCO\underline{CH_3}$); 2.25 (td, 1H, $H_{6'}$, $J_{6',1}$= 3Hz); 3.80 (t, 1H, H_3, $J_{3,4}$= 10Hz); 3.85 (dt, 1H, H_2, $J_{2,3}$= 10Hz); 4.40 (q, 1H, $\underline{CH}CH_3$); 5.10 (m, 1H, H_5, $J_{5,6}$= 14Hz, $J_{5,6'}$= 3Hz); 5.20 (d, 2H, $\underline{CH_2}Ph$); 5.25 (t, 1H, H_4, $J_{4,5}$= 10Hz); 5.60 (broad s, 1H, H_1, $J_{1,2}$= 3Hz); 7.35 (m, 5H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 20.9, 21.0 ($OCO\underline{CH_3}$); 23.1 ($NCO\underline{CH_3}$); 31.5 (C_6); 54.1 (C_2); 67.6 (CH_2Ph); 68.0 (C_5); 69.0 (C_1); 75.3, 75.4 (C_3, C_4); 77.4 ($\underline{CH}CH_3$); 128.3-128.8 (Ph); 169.4-174.9 ($\underline{CO}$).

1D-(1,2,4/3,5)-2-Acetamido-1,4,5-tri-O-acetyl-3-O-[(R)-1'-carboxyethyl]-1,3,4,5-cyclohexanetetrol 14: A solution of ester **13** (1.35 g, 2.74 mol) in ethanol (150 ml) was hydrogenolysed in presence of 0.4 g of palladium on charcoal 10% (2 bars) for 2 h. The solution was filtered on celite pad and evaporated to give the acid **14** which was utilized without futher purification.

1D-(1,2,4/3,5)-2-Acetamido-1,4,5-tri-O-acetyl-3-O-[(R)-2'-propanoyl-L-alanyl-D-isoglutamine benzylester]-1,3,4,5-cyclohexanetetrol 16: To a solution of acid **14** in N, N-dimethylformamide (70 ml) were added N-hydroxysuccinimide (0.43 g, 3.70 mmol) and N, N'-dicyclohexylcarbodiimide (0.76 g, 3.70 mmol). The mixture was stirred for 12 h. The dipeptide **15** was treated with trifluoroacetic acid (4 ml) for 2 h at room temperature and the solution was evaporated to dryness and the residue was dissolved in tetrahydrofuran (20 ml) containing triethylamine (0.52 ml, 7.15 mmol). This solution was added to the activated acid prepared as above. After 12 h., the dicyclohexylurea was filtered off and the solvent was evaporated to give a residue which was purified on a silica gel column (methylene chloride-ethanol, 10:1) and crystallized from chloroform to afford **16** (1.32g, 78%). Anal. Calcd. for C_{32} H_{44} N_4 O_{13}: C, 50.32; H, 7.10; N, 9.03 Found: C, 50.28; H, 7.18; N, 9.10. $[\alpha]_D^{20}$= +20° (c= 2.17, CH_3OH). Mp= 202°C. ^{13}C NMR δ (200 MHz, $CDCl_3$): 18.2 (CH_3-Ala); 19.9 ($\underline{CH_3}CH$); 21.2, 21.3, 21.4 ($CO\underline{CH_3}$); 23.3 ($NHCO\underline{CH_3}$); 26.5 ($CH\underline{CH_2}$-isoGln); 28.9 ($\underline{CH_2}CO$-isoGln); 31.8 (C_6); 51.0 (CH-Ala); 54.0 (CH-isoGln); 55.1 (C_2); 67.9 ($\underline{CH_2}Ph$); 70.7 (C_5); 71.0 (C_1); 77.2 ($\underline{CH}CH_3$); 79.0 (C_3); 79.4 (C_4); 129.7-137.9 (Ph); 172.1-176.3 (CO).

1D-(1,2,4/3,5)-2-Acetamido-3-O-[(R)-2'-propanoyl-L-alanyl-D-iso-glutamine]-1,3,4,5-cyclohexanetetrol 1: A solution of potassium hydroxide (0.205 g, 4.27 mmol.) in water (12.5 ml) was added at O°C to a solution of **16** (0.240 g, 0.35 mmol) in dioxane (12.5 ml). The mixture was stirred for 6 h and neutralized with a resin IRN-77 H^+. The solvents were evaporated and the residue was dissolved in acetic acid (2 mM) and chromatographed on a resin AG1X2 (acetate form) with a gradient of acetic acid as eluant to yield **1** (0.102 g, 61%) after freeze-drying. Anal. Calcd. for $C_{19}H_{32}$ N_4 O_{10}: C, 47.89; H, 6.77, N, 11.76. Found: C, 47.61; H, 6.88; N, 11.91. $[\alpha]_D^{20}$= +30° (c= 0.8, CH_3CH_2OH). ^{13}C NMR δ (200 MHz, $CDCl_3$): 18.0 (CH_3-Ala); 19.7 ($\underline{CH_3}CH$); 22.4 ($NHCO\underline{CH_3}$); 27.1 ($CH\underline{CH_2}$-isoGln); 32.4 ($\underline{CH_2}COOH$-isoGln); 38.0 (C_6); 50.5 (CH-ALa); 53.4 (CH-isoGln); 57.7 (C_2); 67.5, 69.8 (C_1, C_5); 77.7 ($\underline{CH}CH_3$); 79.2, 80.1 (C_3, C_4); 173.4, 174.4, 175.0, 176.6, 178.3 (CO).

1D-(1,2,4/3,5)-2-Amino-1,2-N,O-carbonyl-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 34: A solution of **27** (2.1 g, 4.44 mmol) in dry tetrahydrofuran (10 ml) was added to a blue solution of Li metal in liquid NH_3 (50 ml, dried over Na) at -78°C. Small amounts of Li were added in alternation with the benzyl derivative **27** to maintain the blue color. After 30 mn tert-butyl-alcohol (3 ml) was added dropwise in three portions and then ethanol until the solution turned white. The mixture was diluted with tetrahydrofuran and treated with a resin CG 50 H^+. This mixture was filtered off and concentrated to give **34** (0.9 g) as a yellow foam. The residue was utilized without further purification. MS (CI): 204 (MH^+); 186 (MH^+-H_2O); 160 (MH^+-CO_2). ^{13}C NMR δ (200 MHz, $CDCl_3$): 27.6 (C_6); 38.9 (C_5); 59.2 (C_2); 62.6 (C_7); 71.6 (C_1); 78.4 (C_3, C_4); 162.2 (CO).

1D-(1,2,4/3,5)-2-Amino-1,2-N,O-carbonyl-4,7-benzylidene-5-C-hydroxy-methyl-1,3,4-cyclohexanetriol 35: The triol **34** (0.9 g, 4.43 mmol) was treated with benzaldehyde (30 ml) and zinc chloride (4.7 g, 35.4 mmol). After 72 h at room temperature, the mixture was diluted with ethyl acetate and neutralized with aqueous saturated sodium hydrogen carbonate. The solvents were evaporated. The residue was purified on a silica gel column (ethyl acetate) to afford **35** which was crystallized from ethyl acetate (0.77g, 60%). Anal. Calcd. for C_{15} H_{17} N O_5: C, 61.85; H, 5.88. Found: C, 61.59; H, 5.80. $[\alpha]_D^{20}$= +28° (c= 2.30, CH_3OH). Mp= 196-197°C. ^1H NMR δ (200 MHz, $CDCl_3$): 1.30 (m, 2H, H_6, H_5); 1.57 (m, 1H, $H_{6'}$); 3.47 (q, 1H, H_2); 3.62 (m, 2H, H_4, H_7); 4.17 (dd, 1H, $H_{7'}$); 4.35 (m, 1H, H_3); 4.69 (m, 1H, H_1); 5.66 (s, 1H, $\underline{CH}Ph$); 7.23-7.60 (m, 5H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 26.5 (C_6); 31.6 (C_5); 59.4 (C_2); 70.6 (C_7); 75.5, 75.8 (C_1, C_3); 80.2 (C_4); 101.3 ($\underline{CH}Ph$); 125.4-128.8, 137.8 (Ph); 159.1 (CO).2

1D-(1,2,4/3,5)-2-Amino-1,2-N,O-carbonyl-4,7-benzylidene-3-O-[(R)-2'-propanoyl-L-alanyl-D-isoglutamine benzylester]-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 36: A solution of alcohol **35** (0.4 g, 1.35 mmol) in N, N-dimethylformamide (5 ml) was added at 0°C

under argon to a suspension of sodium hydride (50% in oil) (0.16 g, 3.48 mmol) in N, N-dimethylformamide (1 ml). Then (S)-α-chloropropionic acid (0.2 ml, 1.56 mmol) was added. The mixture was stirred at room temperature for 2 h and diluted with tetrahydrofuran (10 ml), neutralized at 0°C with a resin IRN 77 H^+. The solution was filtered off and the solvents were evaporated to dryness. The residue was purified on a silica gel column (methylene chloride-methanol, 13:2) to yield acid **36** as a colorless oil (0.353 g, 72%). Anal. Calcd. for C_{18} H_{21} N O_7: C, 59.50; H, 5.83; Found: C, 59.64; H, 5.82. $[\alpha]_D^{20}$= +136° (c= 0.34, CH_3OH). ^1H NMR δ (200 MHz, $CDCl_3$): 1.45 (m, 4H, CH_3, H_6); 1.95 (m, 1H, $H_{6'}$); 2.23 (m, 1H, H_5); 3.68 (m, 4H, H_7, $H_{7'}$, H_2, H_4); 4.30 (m, 2H, $\underline{CH}CH_3$, H_3); 4.78 (m, 1H, H_1); 5.70 (m, 1H; $\underline{CH}Ph$); 7.13-7.50 (m, 5H, Ph). ^{13}C NMR δ (200 MHz, $CDCl_3$): 20.0 ($\underline{CH_3}CH$); 26.8 (C_6); 33.0 (C_5); 59.2 (C_2); 71.0 (C_7); 76.3, 76.6 ($CH_3\underline{CH}$, C_1); 81.7 (C_3); 84.4 (C_4); 101.3 ($\underline{CH}Ph$); 127.0, 129.4, 139.7 (Ph); 160.5 (NCO); 177.2 (COOH).

1D-(1,2,4/3,5)-2-Amino-1,2-N,O-carbonyl-3-O-[(R)-2'-propanoyl-L-alanyl-D-isoglutamine benzylester]-5-C-hydroxymethyl-1,3,4-cyclohexane-triol 37: To a solution of acid **36** (0.1 g, 0.275 mmol) in N, N-dimethylformamide (2 ml) were added N-hydroxysuccinimide (0.35 g, 0.303 mmol) and N, N'-dicyclohexylcarbodiimide (0.63 g, 0.303 mmol). The mixture was stirred for 12 h. The dipeptide **15** (0.123 g, 0.303 mmol) was treated with trifluoroacetic acid (2 ml) for 2 h at room temperature and the solution was evaporated to dryness and the residue dissolved in N, N-dimethylformamide (2 ml) containing triethylamine (2 ml). This solution was added to the activated acid prepared as above. After 12 h, the dicyclohexylurea was filtered off and the solvent was evaporated to give a residue which was purified on a silica gel column (methylene chloride-methanol, 10:1) and crystallized from chloroform to yield **37** (0.14 g, 78%). Anal. Calcd. for C_{33} H_{40} N_4 O_{10}: C, 60.73; H, 6.18, N, 8.58. Found: C, 60.50; H, 6.04; N, 8.46. $[\alpha]_D^{20}$= +57° (c= 0.4, CH_3OH). Mp= 233-234°C; ^{13}C NMR δ (200 MHz, $CDCl_3$): 18.4 (CH_3-Ala); 19.5 ($\underline{CH_3}CH$); 26.5 ($CH\underline{CH_2}$-isoGln); 27.3 ($\underline{CH_2}CO$-isoGln); 30.5 (C_6); 31.5 (C_5); 49.3 ($\underline{CH}$-Ala); 52.6 (CH-isoGln); 58.5 (C_2); 66.5 ($\underline{CH_2}Ph$); 70.7 (C_7); 75.8 (C_4); 77.5 ($CH_3\underline{CH}CO$); 81.(C_1); 83.7 (C_3); 101.3 ($\underline{CH}Ph$); 126.0-138.0 (Ph); 159.1, 173.2, 173.8, 174.1 (CO).

1D-(1,2,4/3,5)-2-Amino-1,2-N,O-carbonyl-3-O-[(R)-2'-propanoyl-L-alanyl-D-isoglutamine]-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 2: A solution of ester **37** (0.70 g, 0.107 mol) in ethanol (50 ml) was hydrogenolysed in presence of 0.070 g of palladium on charcoal (10%) (3 bars) overnight. The solution was filtered on celite and evaporated to give the acid **2** which was purified on HPLC column Alltech-RSi (NH_2, 10μ) (acetic acid 0.2N) to afford **2** which was crystallized from ethyl acetate (0.043 g, 84%). Anal. Calcd. for C_{19} H_{30} N_4 O_{10}: C, 48.10; H, 6.37. N, 11.81 Found: C, 48.19; H, 6.47; N, 11.76. $[\alpha]_D^{20}$= +53° (c= 4.3, H_2O). Mp= 142-143°C. ^{13}C NMR δ (200 MHz, $CDCl_3$): 17.8 (CH_3-Ala); 19.6 ($\underline{CH_3}CH$); 28.4, 28.7 ($\underline{CH_2}CO$-isoGln, $CH\underline{CH_2}$-isoGln); 31.7 (C_6); 40.1 (C_5); 50.0, 50.6 (CH-isoGln, CH-Ala); 59.2 (C_2); 63.7 (C_7); 73.1 ($CH_3\underline{CH}$); 78.0 (C_1); 86.3 (C_3).

REFERENCES

1.(a) Barton, D.H.R.; Gero, S.D.; Augy, S.; Quiclet-Sire, B. *J. Chem. Soc. Chem. Comm.*,**1986**, 1399; (b) Barton, D.H.R.; Gero, S.D.; Cleophax, J.; Machado, A.S. and Quiclet-Sire, B.; *J.Chem. Soc. Chem. Comm.* **1988**, 1184; (c) Semeria, D.; Philippe, M.; Delaumeny, J.M.; Sepulchre, A.M. and Gero ,S.D.; *Synthesis* **1983**, 710.

2. Marquez ,V.E. and Ill Lim, Mu *Med. Res. Rev.*,**1986**, 6, 1.

3. McAlpine, J. B.; Egan, R.S.; Stanaszek, R.S.; Cirovic, M.; Mueller, S.L.; Carney, R. E.; Collum, P.; Fager, E.E.; Goldstein, A.W.; Grampovnik, D.J.; Kurath, P.; Martin, J.R.; Post, G.G.; Seely, J.H. and Tadanier, J. In *"Aminocyclitol Antibiotics"* Rinehart, K.L. and Suami, T. Eds American Chemical Society, **1980**, 295.
4. Iwasa, T.; Yamamoto, Y. and Shibata, M. *J. Antibiot.* **1970**, 23, 595.
5. Truscheit, E.; Frommer, W.; Junge, W.; Müller, B.; Schmidt, D.D. and Winsender, W.; *Angew. Chem.,Int. Ed.* **1981**, 20, 744; Junge, B.; Heiker, F.R.; Kurz, J.; Müller, L.; Smith, D.D. and Wunsche, C. *Carbohydr. Res.*,**1984**, 128, 235.
6. Ogawa, S.; Iwasawa, Y.; Toyokuni, T. and Suami, T. *Carbohydr. Res.*,**1985**, 144, 155.
7. Kaluza, G.; Scholtissek, C. *J. Gen. Virol.* **1972**, 14, 251.
8. Ogawa, S.; Toyokuni, T.; Hattori, Y.; Inose, T. and Suami, T. *Carbohydr. Res.* **1986**, 146, 167.
9. Grosheintz, J.M. and Fischer, H.O.L. *J. Am. Chem. Soc.*,**1948**, 70, 1479.
10. Ferrier, R.J. *J. Chem. Soc. Perkin I* , **1979**, 1455.
11. Matsushima, Y. and Park, J.T. *J. Org. Chem.* **1962**, 27, 3581.
12. Lefrancier, P.; Bricas, E. *Bull. Soc. Chem. Biol.*,**1967**, 49, 1257.
13. Matsushima, Y. and Miyazaki,T. *Bull. Chem. Soc. Jpn.* **1965**, 38, 1325;
14. Garegg, P.; Samuelson, B. *J. Chem. Soc. Perkin I* . **1980**, 2866.
15. Philippe, M. *PhD. Thesis* , **1984**, Orsay-Gif-sur-Yvette.
16. Adam, S. *Tetrahedron Lett.* **1988**, 29, 6589.
17. Barton, D.H.R.; Gero, S.D.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc. Chem. Commun.* **1988**, 1372.
18. Whitesides, G.M.; San Filippo, J. *J. Am. Chem. Soc.* **1970**, 92, 6611. Hill, C.L.; Whitesides, G.M. ibid. **1974**, 96, 870.
19. Tadano, K.; Ueno, Y.; Fukabori, Ch.; Hotta, Y.; and Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, 60, 1727.