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Application of 2,3-Aziridino-γ-lactone Methodology Toward the Enantiospecific Synthesis of the (3*S*,4*S*)-Isomer of Dihydroxy-L-glutamic Acid

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Abstract : The formal synthesis of benzyl 2,3-aziridino-*N*-(benzyloxycarbonyl)-2,3-dideoxy-γ-butyrolactone (**21**) from D-ribose is described. Reaction of **21** with excess benzyl alcohol in the presence of boron trifluoride etherate and hydrogenolysis of the product gave (3*S*,4*S*)-dihydroxy-L-glutamic acid ((3*S*,4*S*)-**3**).

Keywords : azides ; aziridines ; glutamic acid ; lactones

Introduction

L-Glutamic acid, the major excitatory neurotransmitter of the central nervous system, acts through two major classes of receptors, the ionotropic or ion-gated (Ca^{2+}, K^+, Na^+) channel receptors and the metabotropic receptors which are coupled to second messenger systems *via* GTP-binding proteins. Each of these major classes is in turn subdivided into several distinct receptor subclasses.[1] In the case of the ionotropic receptors, these subclasses are defined by their selective interactions with *N*-methyl-D-aspartic acid (NMDA receptors), with kainic acid (KA receptors) or with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA receptors) while the metabotropic receptors are grouped into three different subclasses based on their amino acid sequence homology and the nature of the coupling to the metabolic processes regulated by phospholipase C or adenylyl cyclase. The glutamic acid receptors are implicated in such important phenomenon as synaptic plasticity and memory processing.[2] Over-activation of these receptors has also been linked to ischemia, epilepsy and several long-term neurodegenerative syndromes such as Alzheimer's, Huntington's and Parkinson's diseases.[3] In order to discover possible treatments for the latter and, more fundamentally, to understand the physiological importance of each of the many subclasses of glutamic acid receptors, much effort has been made in recent years to design and synthesize subclass-selective ligands. Among these, substituted, optically pure derivatives of glutamic acid itself have received considerable attention.[4] Both the nature and the stereochemistry of these substituents have been shown to influence binding affinities and, therefore, selectivities for a particular glutamic acid receptor subclass.

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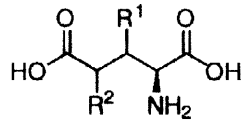
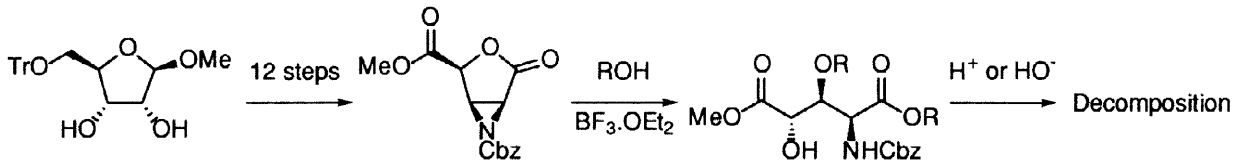
While a large number of alkyl substituted derivatives of glutamic acid have been synthesized[4] and, in some cases, their interactions with glutamic acid receptors investigated, hydroxy and alkoxy derivatives have been less studied. With respect to developing subclass-selective ligands, such compounds present possible accessory hydrogen-bonding interactions with the binding site. Moreover, it can be expected that such hydroxy or alkoxy substituents will allow intramolecular hydrogen bonding interactions with the carboxylate or amine functionalities of glutamic acid, thereby producing conformationally-constrained analogues. One of the richest sources of high-affinity, subclass-selective ligands of glutamic acid receptors has in fact been such conformationally rigid derivatives in which the rigidity is obtained by covalent rather than hydrogen bonds.[5]

While methodology has been developed over the years for the synthesis of optically active β-hydroxy[6] (**1**) and γ-hydroxyglutamic acid[7] (**2**) derivatives, no synthesis of a β,γ-dihydroxyglutamic acid (DHGA, **3**) has been reported, enantiospecific or otherwise, despite the fact that such a compound (of unknown configuration)



1 R^1 = OH, R^2 = H
2 R^1 = H, R^2 = OH
3 R^1 = R^2 = OH

was isolated from various plants over 40 years ago.[8] We recently presented the synthesis of the 2,3-aziridino-γ-lactone-4-methyl ester **5** starting from the simple ribofuranoside derivative **4** (Scheme 1) and showed how, in the presence of alcohols and boron trifluoride etherate, both aziridine and lactone ring opening occur to give the protected 3-alkoxy-4-hydroxy L-glutamate **6**.[9d] The latter, in the case where benzyl alcohol is used as the nucleophile, appeared to be an ideal precursor of one of the four possible stereoisomers of DHGA **3**. Unexpectedly, while the benzyl and benzyloxycarbonyl (Cbz) protecting groups of **6** could be easily removed by hydrogenolysis, hydrolysis of the methyl ester under either acidic or basic conditions led to extensive decomposition. An obvious solution to this problem would be to prepare the benzyl ester analogue of the methyl ester **5** which would then allow all the blocking groups to be removed by hydrogenolysis. However, this would require a modification of the reaction conditions previously used for the preparation of the aziridine ring,

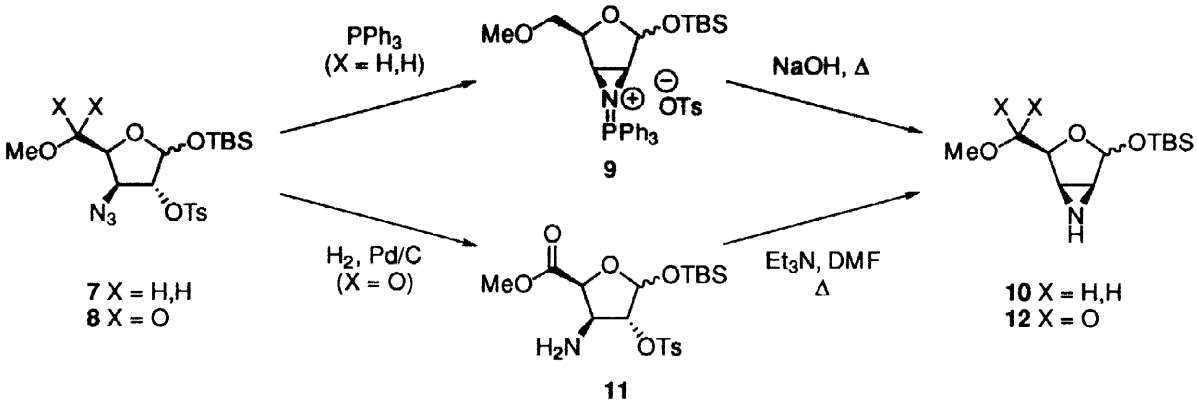


4 **5** **6**

Scheme 1

incompatible with the presence of a benzyl ester functionality on the substrate. Thus, in our general route to aziridino-γ-lactones from ribose (or lyxose), a key intermediate was the 2-*O*-tosyl-3-azido derivative of type **7** or **8** (Scheme 2). In the case of the 5-*O*-methyl ether compound **7**, aziridine ring formation was obtained by a Staudinger-type reaction using triphenylphosphine.[9a] The intermediate phosphiniminium salt **9** formed in this reaction was then hydrolyzed to the aziridine **10** with hot aqueous sodium hydroxide. In the case of the methyl

ester **8**, in which the use of sodium hydroxide is proscribed, aziridine formation was obtained by catalytic hydrogenation of the azide to the amine **11** followed by triethylamine promoted cyclization to **12** in hot DMF.[9d]

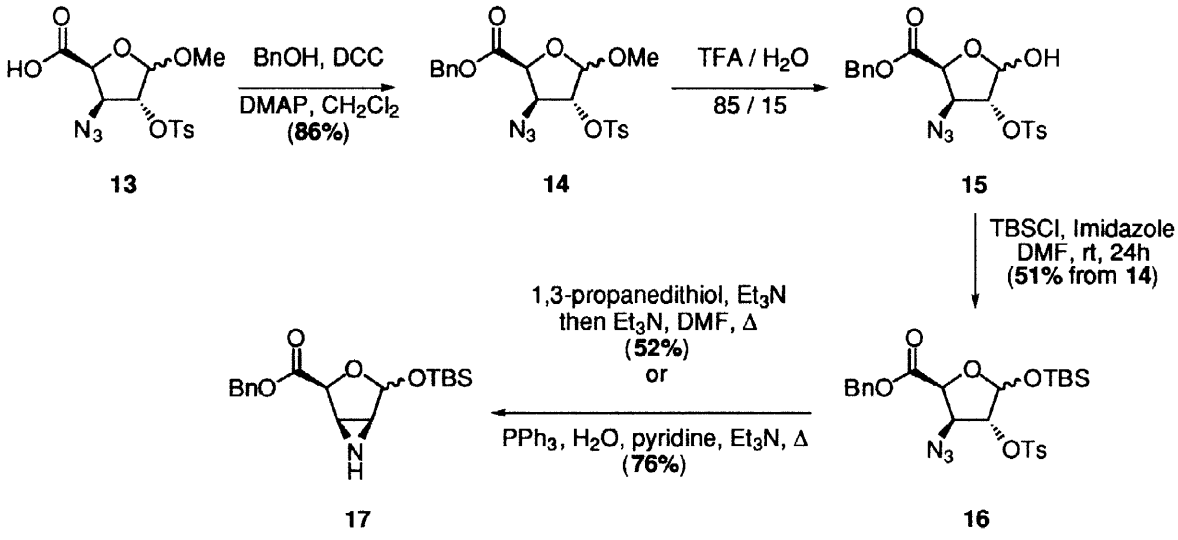


Scheme 2

In this communication, then, we present two solutions to the problem of forming an aziridine ring from an azido-tosyl precursor in the presence of a benzyl ester, thereby permitting the first stereocontrolled preparation of a fully deprotected DHGA (3*S*,4*S*-**3**).

Results and Discussion

The starting material for our study was the uronic acid derivative **13** (α,β mixture, Scheme 3) previously synthesized by us from D-ribose in 6 steps and 42% overall yield for the preparation of methyl ester **5**.[9d] Compound **13** was transformed into the benzyl ester **14** in 86% yield by treatment with benzyl alcohol, DCC and catalytic DMAP in dichloromethane. At this point and by analogy with our previously successful strategy for aziridino-γ-lactone synthesis, the anomeric methoxy function must be converted into a silyl ether function, removable in the presence of the projected aziridine ring.



Scheme 3

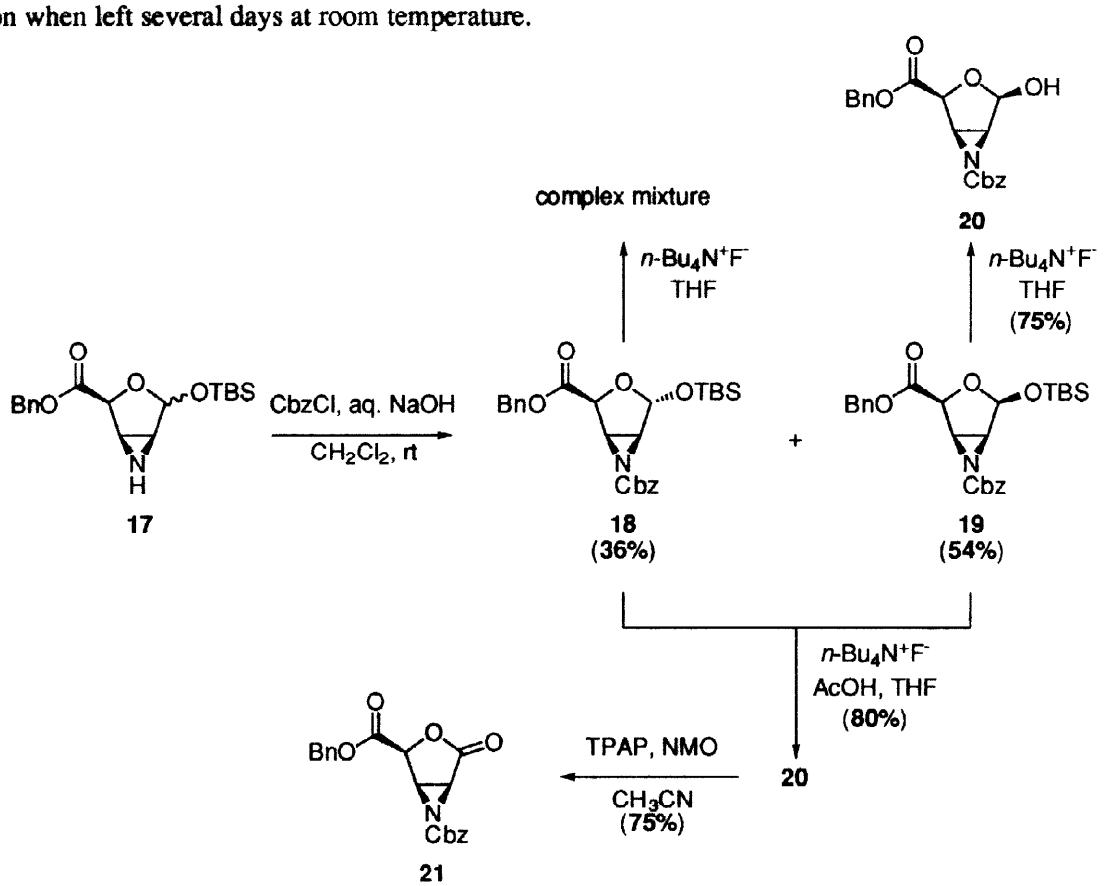
Acid hydrolysis of **14** using aqueous trifluoroacetic acid gave, after 65 h at room temperature, the furanose **15** in 75% yield. Though some starting material remained at the end of the reaction, use of longer reaction times or higher temperatures led to considerable hydrolysis of the benzyl ester function. While this contaminant could be removed by chromatography of the crude reaction mixture of **15**, it was found to be more convenient to proceed directly to silylation of this crude product utilizing *tert*-butyldimethylsilyl chloride and imidazole in DMF. Chromatography of the products of this reaction then afforded the *O*-silyl furanoside **16** in 51% yield and permitted recovery of unhydrolyzed methyl furanoside **14** (25%).

With compound **16** in hand, reductive cyclization of the azide in the presence of the benzyl ester could be attempted.[10] Corey has reported the use of Lindlar catalyst in ethanol for the selective hydrogenation of azides in the presence of double bonds.[11] Applied to compound **16**, however, these conditions led to simultaneous reduction of the azide and hydrogenolysis of the benzyl ester. The use of a less polar solvent than ethanol did, however, result in some selectivity. Thus, hydrogenation of **16** in ethyl acetate for 5 h at 20°C in the presence of Lindlar catalyst followed by triethylamine-promoted cyclization of the crude product in DMF at 110°C for 4 h led to a 25% yield of aziridine benzyl ester **17**. The aziridine ring of **17** gave rise to the characteristic high-field signal (2.6-2.9 ppm) in the ^{1}H NMR spectrum. Unfortunately, use of solvents other than ethyl acetate, shorter reaction times or lower temperatures did not allow improvements in the yield of **17**.

1,3-Propanedithiol is a reagent which was reported some time ago to promote reduction of azides to amines in the presence of reduction-sensitive functions (double and triple bonds, nitro groups).[12] When **16** was treated in two cycles with excess 1,3-propanedithiol and triethylamine in methanol at room temperature (total reaction time of 2.5 h), and the crude amine was cyclized as before (triethylamine, DMF, 110°C, 4 h), the desired aziridine **17** was obtained in the somewhat more satisfactory yield of 52% after careful chromatographic purification of the complex reaction mixture.[13]

In a effort to further improve the yield and the ease of purification of aziridine **17**, a key synthon in our approach to amino acid synthesis, our original methodology used to prepare a bicyclic aziridine structure (i.e. **10**, Scheme 2) from a *trans* azido tosylate (**7**) *via* a modified Staudinger reaction was re-evaluated. It seemed reasonable to assume that if formation of the intermediate triphenylphosphiniminium species **9** could be avoided after treatment of the azido tosylate with triphenylphosphine, then this would obviate the need for the subsequent, drastic hydrolysis step. Vaultier and coworkers have shown that azides can be efficiently converted to amines by triphenylphosphine in THF in the presence of a slight excess of water.[14] The latter serves to hydrolyze the intermediate phosphinimine as it forms. In view of these results, azido tosylate **16** in THF was treated at room temperature with triphenylphosphine in the presence of water (1.4 eq.). Transformation to the amine was effectively complete within 22 h. Moreover, approximately 10% of the desired aziridine **17** (as evaluated by ^{1}H NMR spectroscopy of the crude reaction mixture) was formed in the process. An attempt was thus made to prepare aziridine **17** in a single step from **16** by performing the reaction in hot pyridine instead of THF. Under these conditions, aziridine **17** was the major product formed. Finally, after some experimentation, it was found that up to 76% yields of aziridine **17** could be obtained by heating azide **16** in pyridine for 15 h at 90°C in the presence of a slight excess of triphenylphosphine, 2.3 eq. of water and 8 eq. of triethylamine.

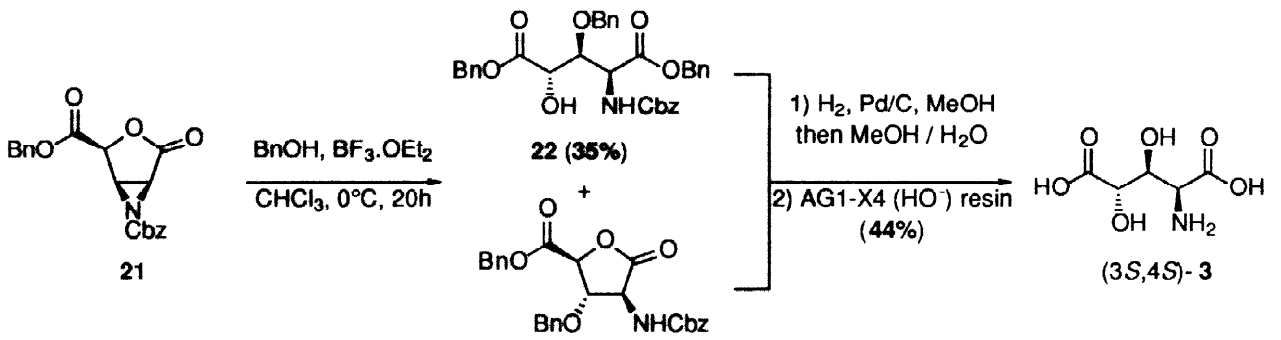
Treatment of aziridine **17** with benzylchloroformate in a biphasic mixture of dichloromethane and aqueous sodium hydroxide then gave the N-Cbz derivative as a 2:3 mixture of the α- and β-anomers (**18** and **19**, respectively) (Scheme 4). Up to this point, no effort had been made to separate the α- and β-anomers since ultimately the C-1 chiral center would be eliminated by oxidation to the lactone. However, when the mixture of **18** and **19** was desilylated using tetrabutylammonium fluoride in THF, only modest yields of product were obtained which, moreover, was only isolated in the form of the β-furanose **20**. In view of this, it was decided to separate anomers **18** and **19** by chromatography on silica gel (using heptane-ethyl acetate 4:1) and investigate the behavior of each isomer in the presence of fluoride anion. It was found that while the β-anomer **19** gave a 75% yield of β-furanose **20**, the α-anomer **18**, under the same reaction conditions, gave a complex mixture of unidentified products. However, addition of 1 eq. of acetic acid to the reaction medium allowed isolation of 80% of the β-hydroxy anomer **20** from the mixture of **18** and **19**. The acetic acid presumably serves to buffer the basic reaction mixture. Finally, the desired aziridino-γ-lactone **21** was obtained in 75% yield by TPAP oxidation of compound **20** in acetonitrile.[15] While compound **21**, an oil, is stable at 0-4°C, it tended to take on an orange coloration when left several days at room temperature.



Scheme 4

Conversion of compound **21** into the desired DHGA was then straightforward (Scheme 5). Thus, the aziridino-γ-lactone in chloroform was first treated with excess benzyl alcohol for 20 h at 0°C in the presence of 2 eq. of boron trifluoride etherate, producing a 1:1 mixture of the 3-*O*-benzyl-4-hydroxyglutamate **22** and its lactonized derivative **23** separated by chromatography. Although it could be reasoned that the presence of lactone **23** is the result of incomplete reaction of **21**, we have previously shown that, in the presence of alcohols,

the lactone ring of aziridino-γ-lactones is opened before the aziridine ring.[9c] Compound **23** is thus more likely the product of partial recyclization of amino acid **22**. In view of this ease of cyclization, it was decided to conduct the final hydrogenolytic deprotection step on the unseparated mixture of **22** and **23**. This was effected at atmospheric pressure using palladium on carbon as catalyst in neat methanol for 2 h and then in a 1:1 mixture of methanol-water for 1.5 h. The crude reaction products, presumably a mixture of DHGA and deprotected lactone **23**, was then purified by passage through a basic anion exchange column (AG1-X4) providing only the "open" form,[16] (3*S*,4*S*)-**3** [(3*S*,4*S*)-DHGA], in 44% yield (based on **22** + **23**).[17,18]



Scheme 5

Conclusion

Use of 2,3-aziridino-γ-lactone methodology which we have previously developed for the preparation of non-natural amino acids has now been successfully applied to the enantiospecific synthesis of (3*S*,4*S*)-dihydroxy-L-glutamic acid. While this methodology is obviously not adapted to the preparation of all the possible stereoisomers of DHGA (notably, the *syn*-dihydroxy derivatives), compound **3** can be considered a starting material for a large variety of novel mono- and di-alkoxy glutamic acid derivatives inaccessible by other means, as will be described in a forthcoming publication.

Experimental Section

General. Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra of samples were obtained either as KBr pellets or as films with a Nicolet 205 FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR were determined on a Bruker 200, 250 or 300 MHz instrument. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization mass spectra were recorded on an AEI MS-50 and AEI MS-9 spectrometer, respectively. High-resolution mass spectra were obtained using a Kratos MS-80 spectrometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Thin-layer chromatography was performed on Merck silica gel plates with fluorescent indicator. The plates were visualized with UV light (254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230-400 mesh) at medium pressure (200 mbar). All reagents were purchased from the Aldrich Chemical Co. and were used without further purification. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette.

Benzyl [Methyl 3-azido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-α, β-D-xylofuranosid]uronate (14). To a solution of compound **13** (7.4 g, 20.7 mmol) in anhydrous CH_2Cl_2 (36 mL) held at 5°C under argon was successively added DMAP (280 mg, 2.3 mmol), benzyl alcohol (2.4 mL, 23.2 mmol) and DCC (5.22 g, 25.3 mmol). The reaction mixture was stirred for 5 min at 5°C and then it was allowed to warm to rt. Stirring was maintained for 5 h, the precipitate which formed was removed by filtration through Celite® and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (heptane-EtOAc 3:1 until elution of the excess benzyl alcohol, followed by 2:1), affording compound **14,** a lightly colored oil (8.0 g, 86%), as an inseparable mixture of α and β anomers (2:3, respectively) : IR (film) 2121, 1762, 1182 cm^{-1} ; mass spectrum (CI) m/z 448 $(MH)^+$, 420 $(MH-N_2)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 2.45, 2.46 (2 x s, 3H, α and β anomer), 3.32 (s, 1.2 H, α anomer), 3.39 (s, 1.8 H, β anomer), 4.34 (d, $J_{3,4}$ = 6.5 Hz, 0.6 H, β anomer), 4.48 (pseudo t, $J_{3,2}$ = $J_{3,4}$ = 7.7 Hz, 0.4 H, α anomer), 4.64 (dd, $J_{2,1}$ = 4.3 Hz, $J_{2,3}$ = 7.3 Hz, 0.4 H, α anomer), 4.74 (d, $J_{4,3}$ = 8.1 Hz, 0.4 H, α anomer), 4.78 (s, 0.6 H, β anomer), 4.93 (d, $J_{4,3}$ = 6.6 Hz, 0.6 H, β anomer), 4.95 (s superimposed on d, $J_{1,2}$ = 4.3 Hz, 1H, α and β anomer), 5.20 (2 x d, J_{gem} = 12.0 Hz, 2H, α and β anomer), 7.34-7.40 (m, 7H), 7.80 (d, J = 8.3 Hz, 2H, α and β anomer) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 22.5, 56.5, 56.6, 64.2, 66.0, 68.1, 68.3, 75.9, 80.9, 81.1, 85.5, 101.3, 107.9, 128.8, 129.4, 129.5, 130.8, 131.1, 133.1, 135.5, 135.7, 146.8, 168.5, 168.7. Anal. Calcd for $C_{20}H_{21}N_3O_7S$. 0.1 H_2O : C, 53.47 ; H, 4.76 ; N, 9.35 ; S, 7.14. Found : C, 53.21 ; H, 4.75 ; N, 9.51 ; S, 7.31.

Benzyl 3-Azido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-α,β-D-xylofuranuronate (15). A solution of compound **14** (4.79 g, 10.7 mmol) in trifluoroacetic acid and water (100 mL of an 85:15 mixture) was stirred at 20°C for 65 h. The reaction mixture was then evaporated under reduced pressure at a bath temperature not exceeding 40°C, the residue was treated with saturated aqueous $NaHCO_3$ (50 mL) and the mixture was extracted with EtOAc (2 x 150 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated under reduced pressure leaving an orange colored syrup (3.7 g) containing 75% of compound **15** (2:3 mixture of α and β anomers, respectively) and 25% of unreacted starting material **14** (as estimated by ^1H NMR). This material was used in the following step without further purification. An analytical sample of **15** was obtained by column chromatography of an aliquot on silica gel (heptane-EtOAc 3:1) : IR (film) 3460, 2121, 1750, 1177 cm^{-1} ; mass spectrum (CI) m/z 434 $(MH)^+$, 406 $(MH-N_2)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 2.46 (s, 3H, α and β anomer), 3.86 (m, 0.4 H, exchangeable with D_2O, α anomer), 4.22 (m, 0.6 H, exchangeable with D_2O, β anomer), 4.49 (dd, $J_{3,2}$ = 2.0 Hz, $J_{3,4}$ = 6.9 Hz, 0.6 H, β anomer), 4.53 (dd, $J_{3,2}$ = 5.8 Hz, $J_{3,4}$ = 7.2 Hz, 0.4 H, α anomer), 4.65 (dd, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 5.8 Hz, 0.4 H, α anomer), 4.76 (d, $J_{2,3}$ = 2.0 Hz, 0.6 H, β anomer), 4.87 (d, $J_{4,3}$ = 7.2 Hz, 0.4 H, α anomer), 4.93 (d, $J_{4,3}$ = 6.9 Hz, 0.6 H, β anomer), 5.20 (2 x d, J_{gem} = 11.9 Hz, 0.8 H, α anomer), 5.24 (s, 1.2 H, β anomer), 5.29 (m, 0.6 H, β anomer), 5.58 (m, 0.4 H, α anomer), 7.36 (m, 7H, α and β anomer), 7.82 (d, J = 8.3 Hz, 2H, α and β anomer) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 21.8, 63.9, 65.6, 67.6, 68.2, 75.7, 80.2, 80.7, 86.0, 95.1, 101.7, 128.0, 128.1, 128.7, 128.8, 128.9, 130.2, 130.3, 132.3, 134.4, 146.1, 169.8. Anal. Calcd for $C_{19}H_{19}N_3O_7S$: C, 52.65 ; H, 4.42 ; N, 9.69 ; S, 7.40. Found : C, 52.35 ; H, 4.54 ; N, 9.72 ; S, 7.39.

Benzyl [*tert*-Butyldimethylsilyl 3-azido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-α,β-D-xylofuranosid]uronate (16). A solution of crude compound **15** (3.7 g) in anhydrous DMF (40 mL) was treated successively at rt with imidazole (1.09 g, 16.0 mmol) and *tert*-butyldimethylsilyl chloride (1.61 g, 10.7 mmol). The reaction mixture was stirred for 24 h, the solvent was removed under reduced pressure and the residue was taken up in EtOAc (150 mL). The solution was washed with water (100 mL), dried (Na_2SO_4) and

the solvent evaporated *in vacuo*. Purification of the residue by chromatography on silica gel (heptane-EtOAc 4:1 followed by 3:1) provided compound **16** as a colorless oil (3.03 g, 51% from **14**) : IR (film) 2118, 1765, 1177 cm^{-1} ; mass spectrum (CI) m/z 548 $(MH)^+$, 520 $(MH-N_2)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 0.03, 0.08 (2 x s, 3.6 H, β anomer), 0.10, 0.12 (2 x s, 2.4 H, α anomer), 0.82 (s, 5.4 H, β anomer), 0.89 (s, 3.6 H, α anomer), 2.46 (s, 3H, α and β anomer), 4.26 (d, $J_{3,4}$ = 5.5 Hz, 0.6 H, β anomer), 4.51 (m, 0.8 H, α anomer), 4.67 (s, 0.6 H, β anomer), 4.79 (m, $J_{4\beta,3}$ = 5.9 Hz, 1H, α and β anomer), 5.19 (2 x d, J_{gem} = 12.0 Hz, 0.8 H, α anomer), 5.21 (2 x d, J_{gem} = 12.1 Hz, 1.2 H, β anomer), 5.28 (s, 0.6 H, β anomer), 5.49 (d, $J_{1,2}$ = 2.9 Hz, 0.4 H, α anomer), 7.36 (m, 7H), 7.81 (d, J = 8.3 Hz, 2H, α and β anomer) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ -4.8, -4.6, 17.9, 21.7, 25.4, 25.5, 63.2, 64.7, 67.2, 67.5, 75.0, 79.8, 81.2, 86.1, 94.9, 101.7, 128.0, 128.5, 128.6, 128.7, 130.0, 130.3, 132.6, 132.7, 135.1, 145.5, 145.9, 167.2, 168.2. Anal. Calcd. for $C_{25}H_{33}N_3O_7SSi$. 0.02 H_2O : C, 54.47 ; H, 6.11 ; N, 7.62 ; S, 5.82. Found : C, 54.23 ; H, 6.02 ; N, 7.82 ; S, 6.01.

Continued elution of the chromatography column with heptane-EtOAc (3:1) afforded the unreacted methyl furanoside **14** (1.19 g, 25%).

Benzyl (*tert*-Butyldimethylsilyl 2,3-aziridino-2,3-dideoxy-α,β-D-lyxofuranosid)uronate (17). *1,3-Propanedithiol method* : A solution of compound **16** (2.63 g, 4.8 mmol) in anhydrous MeOH was treated at rt with triethylamine (1.01 mL, 7.2 mmol) and 1,3-propanedithiol (0.72 mL, 7.2 mmol). The reaction mixture was stirred for 1h, fresh triethylamine (1.01 mL, 7.2 mmol) and 1,3-propanedithiol (0.72 mL, 7.2 mmol) were added and stirring was continued for 1.5 h. The solvents and excess reagents were removed under reduced pressure, the oily yellow residue was dissolved in DMSO (52 mL) and triethylamine (9 mL) and the solution was heated at 120°C for 8 h. Evaporation of the solvents under reduced pressure left a crude product which was purified by column chromatography on silica gel (heptane-EtOAc 3:1) affording compound **17** as an orange-colored oil (450 mg, 52%) ; IR (film) 3280, 2960, 1755, 1250 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 0.13 (s, 3H, α and β anomer), 0.14 (s, 3H, α and β anomer), 0.90 (s, 9H, α and β anomer), 2.60 (m, 0.4 H, α anomer), 2.67 (d, $J_{2,3}$ = 3.0 Hz, 0.6 H, β anomer), 2.83 (dd, $J_{3,2}$ = 3.0 Hz, $J_{3,4}$ = 1.9 Hz, 0.6 H, β anomer), 2.93 (m, 0.4 H, α anomer), 4.45 (d, $J_{4,3}$ = 1.9 Hz, 0.6 H, β anomer), 4.65 (d, $J_{4,3}$ = 1.7 Hz, 0.4 H, α anomer), 5.22 (2 x d, J_{gem} = 12.3 Hz, 1.2 H, β anomer), 5.24 (2 x d, J_{gem} = 12.2 Hz, 0.8 H, α anomer), 5.45 (s, 0.4 H, α anomer), 5.50 (s, 0.6 H, β anomer), 7.36 (s, 5H, α and β anomer) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.4, -4.3, 18.0, 25.7, 35.6, 36.7, 38.6, 39.5, 67.1, 67.2, 74.9, 75.0, 98.3, 98.4, 128.0, 128.3, 128.4, 128.5, 128.6, 135.2, 168.8, 168.9 ; mass spectrum (HRCI) calcd for $C_{18}H_{28}NO_4Si$ $(MH)^+$ m/z 350.1788, found 350.1786.

Triphenylphosphine method : A solution of compound **16** (1.35 g, 2.46 mmol) in pyridine (5.5 mL) was treated successively with triphenylphosphine (775 mg, 2.95 mmol), water (130 μL, 7.4 mmol) and triethylamine (2.6 mL, 19.7 mmol). The reaction mixture was heated at 90°C for 15 h, the solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (heptane-EtOAc 3:1) affording compound **17** as an orange-colored oil (660 mg, 76%) identical in all respects with that obtained by the previous method.

Benzyl [*tert*-Butyldimethylsilyl 2,3-aziridino-*N*-(benzyloxycarbonyl)-2,3-dideoxy-α-(and β-)-D-lyxo-furanosid]uronate (18 and 19). A solution of compound **17** (560 mg, 1.6 mmol) in anhydrous CH_2Cl_2 (6 mL) was treated successively at rt with aqueous NaOH (2.4 mL of a 1 M solution ; 2.4 mmol) and benzyl chloroformate (250 μL, 1.7 mmol). The reaction mixture was stirred vigorously for 1 h and then washed with water (20 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure

leaving a crude product which was purified by column chromatography on silica gel (heptane-EtOAc 4:1 then 2:1). The first compound to be eluted was the α anomer **18** (280 mg, 36%) which crystallized on standing : mp 70-71°C ; $[\alpha]_D^{21}$ -18.1° (c 2.0, $CHCl_3$) ; IR (film) 1765, 1735 cm^{-1} ; mass spectrum (CI) m/z 484 $(MH)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.14 (s, 3H), 0.87 (s, 9H), 3.17 (dd, $J_{2,1}$ = 0.7 Hz, $J_{2,3}$ = 3.9 Hz, 1H), 3.55 (dd, $J_{3,2}$ = 3.9 Hz, $J_{3,4}$ = 1.7 Hz, 1H), 4.65 (d, $J_{4,3}$ = 1.7 Hz, 1H), 4.91 (d, J_{gem} = 12.2 H, 1H), 4.92 (d, J_{gem} = 12.2 Hz, 1H), 5.11 (d, J_{gem} = 12.2 Hz, 1H), 5.52 (d, J_{gem} = 12.2 Hz, 1H), 5.55 (s, 1H), 7.35 (m, 10H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.3, 17.8, 25.6, 40.5, 43.7, 66.9, 68.2, 73.9, 96.1, 128.3, 128.4, 128.5, 135.3, 135.4, 159.7, 167.4.

Continued elution of the chromatography column afforded the major β anomer **19** (418 mg, 54%) which crystallized in heptane-EtOAc : mp 78-79°C ; $[\alpha]_D^{21}$ -41.3° (c 2.0, $CHCl_3$) ; IR (film) 1765, 1735 cm^{-1} ; mass spectrum (CI) m/z 484 $(MH)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 0.15 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 3.32 (dd, $J_{2,1}$ = 1.3 Hz, $J_{2,3}$ = 4.6 Hz, 1H), 3.55 (dd, $J_{3,2}$ = 4.6 Hz, $J_{3,4}$ = 2.3 Hz, 1H), 4.41 (d, $J_{4,3}$ = 2.3Hz, 1H), 5.12 (2 x d, J_{gem} = 12.4, 2H), 5.19 (2 x d, J_{gem} = 12.3 Hz, 2H), 5.45 (d, $J_{1,2}$ = 1.3 Hz, 1H), 7.32 (m, 10H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.2, 18.1, 25.7, 42.0, 44.0, 67.0, 68.3, 74.6, 97.4, 128.0, 128.2, 128.3, 128.4, 128.5, 135.4, 135.5, 161.1, 167.5. Anal. Calcd for $C_{26}H_{33}NO_6Si$: C, 64.57 ; H, 6.88 ; N, 2.90. Found : C, 64.43 ; H, 7.06 ; N, 2.86.

Benzyl 2,3-Aziridino-*N*-(benzyloxycarbonyl)-2,3-dideoxy-β-D-lyxofuranuronate (20). To a solution of compound **18** and **19** (1.26 g, 2.6 mmol) in THF (17 mL) was added, at -60°C under argon, a solution of tetrabutylammonium fluoride in THF (2.86 mL of a 1M solution ; 2.86 mmol) followed by acetic acid (161 μL, 2.86 mmol). The reaction mixture was allowed to come to rt over 80 min and then the solvent was removed under reduced pressure. Purification of the residue by column chromatography on silica gel (heptane-EtOAc 2:1 then 3:2) afforded compound **20** (770 mg, 80%) as a colorless oil : $[\alpha]_D^{21}$ -60.1° (c 0.4, $CHCl_3$) ; IR (film) 3450, 1750, 1731 cm^{-1} ; mass spectrum (CI) m/z 370 $(MH)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 3.25 (d, $J_{2,3}$ = 3.8 Hz, 1H), 3.56 (dd, $J_{3,2}$ = 3.8 Hz, $J_{3,4}$ = 1.8 Hz, 1H), 4.45 (m, 1H, exchangeable with D_2O), 4.74 (d, $J_{4,3}$ = 1.8 Hz, 1H), 4.88 (d, J_{gem} = 12.2 Hz, 1H), 4.91 (d, J_{gem} = 12.1 Hz, 1H), 5.07 (d, J_{gem} = 12.2 Hz, 1H), 5.18 (d, J_{gem} = 12.1 Hz, 1H), 5.64 (m, 1H), 7.33 (m, 10H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 42.6, 67.2, 68.4, 73.9, 95.5, 127.6, 128.0, 128.5, 128.6, 135.0, 135.2, 159.8, 167.9. Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03 ; H, 5.18 ; N, 3.79. Found : C, 64.69 ; H, 5.16 ; N, 3.81.

(1*S*,4*S*,5*R*)-4,*N*-(Dibenzyloxycarbonyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (21). To a mixture of 4-methylmorpholine *N*-oxide (118 mg, 1.0 mmol) (previously dried under vacuum at 90°C) and freshly activated, powdered 4 Å molecular sieves (335 mg) was added at rt under argon a solution of compound **20** (248 mg, 0.67 mmol) in acetonitrile (7 mL) followed by solid TPAP (34 mg, 0.1 mmol). The reaction mixture was stirred for 2.5 h and the solvent was then removed under reduced pressure. The residue, dissolved in EtOAc, was filtered through a pad of silica gel, leaving, after evaporation of the filtrate, pure compound **21** (185 mg, 75%) as a faintly colored oil which exhibited a tendancy to decompose at rt :$[\alpha]_D^{22}$ -30.1° (c = 2.0, $CHCl_3$) ; IR (film) 1806, 1762, 1738 cm^{-1} ; mass spectrum (CI) m/z 368 $(MH)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 3.57 (d, $J_{1,5}$= 4.0 Hz, 1H), 3.98 (pseudo t, $J_{5,1}$ = $J_{5,4}$ = 3.6 Hz, 1H), 4.98 (d, $J_{4,5}$ = 3.6 Hz, 1H), 5.05 (d, J_{gem} = 12.1 Hz, 1H), 5.13 (d, J_{gem} = 12.0 Hz, 1H), 5.14 (d, J_{gem} = 12.0 Hz, 1H), 5.22 (d, J_{gem} = 12.1 Hz, 1H), 7.32 (m, 10H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.0, 41.4, 68.1, 69.6, 75.0, 128.5, 128.6, 128.7, 128.9, 134.7, 158.4, 165.0, 167.2.

Dibenzyl (2*S*,3*S*,4*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-benzyloxy-4-hydroxypentane-1,5-dioate (22) and Benzyl (2*S*,3*S*,4*S*)-Tetrahydro-4-[*N*-(benzyloxycarbonyl)amino]-3-benzyloxy-5-oxo-2-furancarboxylate (23). To a solution of compound **21** (110 mg, 0.3 mmol) and benzyl alcohol (254 µL, 2.4 mmol) in $CHCl_3$ (3 mL) was added, at 0°C under argon, boron trifluoride etherate (73 µL, 0.6 mmol). The reaction mixture was stirred at 0°C for 20 h and, after dilution with EtOAc (15 mL), it was washed with aqueous $NaHCO_3$ (5 mL of a 0.5 M solution). The aqueous phase was extracted with EtOAc (2 x 15 mL), the organic extracts were combined, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using heptane-EtOAc (5:1) as developer. Compound **23**, obtained as a white solid (60 mg, 34%) was the first to be eluted : mp 125°C ; $[\alpha]_D^{22}$ + 15.8° (c 0.6, $CHCl_3$) ; IR (film) 3360, 1806, 1743, 1725, 1520 cm-1; mass spectrum (CI) m/z 476 $(MH)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 4.37 (m, 2H), 4.61 (m, 2H), 4.83 (d, $J_{2,3}$ = 3.8 Hz, 1H), 5.33 (d, $J_{NH,4}$ = 6.1 Hz, 1H, exchangeable with D_2O), 7.18-7.36 (m, 15H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.7, 68.4, 68.8, 73.3, 79.3, 81.5, 128.7, 128.9, 129.0, 129.1, 129.2, 129.3, 129.5, 135.3, 136.8, 137.3, 157.2, 168.2, 172.1.

Continued elution of the chromatography column provided compound **22** (50 mg, 35%) which crystallized as a white powder in heptane-EtOAc : mp 84-85°C ; $[\alpha]_D^{28}$ +12.6° (c 0.5, $CHCl_3$) ; IR (film) 3450, 3360, 1730, 1525 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (d, $J_{OH,4}$ = 6.5 Hz, 1H, exchangeable with D_2O), 4.08 (d, J_{gem} = 11.0 Hz, 1H), 4.15 (dd, $J_{4,3}$ = 7.6 Hz, $J_{4,OH}$ = 6.5 Hz, 1H), 4.22 (d, J_{gem} = 11.0 Hz, 1H), 4.25 (dd, $J_{3,2}$ = 1.3 Hz, $J_{3,4}$ = 7.6 Hz, 1H), 4.81 (dd, $J_{2,3}$ = 1.3 Hz, $J_{2,NH}$ = 9.0 Hz, 1H), 5.08-5.12 (m, 5H), 5.19 (d, J_{gem} = 12.1 Hz, 1H), 5.70 (d, $J_{NH,2}$ = 9.0 Hz, 1H, exchangeable with D_2O), 6.97-7.37 (m, 20H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.6, 67.5, 67.6, 67.7, 70.6, 73.9, 80.7, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 134.7, 134.9, 135.8, 136.9, 157.1, 170.3, 171.9 ; mass spectrum (HRCI) calcd for $C_{34}H_{34}NO_8$ $(MH)^+$ m/z 584.3224, found 584.3239.

(3*S*,4*S*)-Dihydroxy-L-glutamic acid (3). A mixture of compounds **22** and **23** (100 mg, ~ 0.19 mmol) and 10% palladium on carbon (90 mg) in MeOH (15 mL) was hydrogenolyzed at atmospheric pressure and at rt for 2 h. The reaction mixture was then concentrated under reduced pressure, water and MeOH (12 mL of a 1:1 mixture) followed by fresh palladium on carbon (90 mg) were added and hydrogenolysis was continued for another 1.5 h. The reaction mixture was then filtered through Celite®, the filter pad was washed with a mixture of hot water and MeOH (1:1) and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by ion-exchange chromatography as follows : AG1-X4 resin (700 mg, OH^- form) was placed in a cotton-plugged pasteur pipette and washed with acetic acid (10 mL of a 1 M solution) and with water until neutral pH (10-15 mL). A solution of the crude product in water (10 mL) was brought to pH 9 by addition of 1M NaOH and then applied to the resin. The column was first eluted with water until neutrality (10-15 mL) and then successively with 0.2 M (10 mL), 0.3 M (10 mL), 0.4 M (10 mL) and 0.5 M (20 mL) aqueous acetic acid. The ninhydrin-positive fractions were combined, evaporated under reduced pressure at 35°C and the residue was lyophilized for 24 h, affording compound **3** (15 mg, 44%) as an amorphous white solid : $[\alpha]_D^{28}$ -0.8° (c 1.0, H_2O) ; mass spectrum (FAB) m/z 180 $(MH)^+$; ^1H NMR (250 MHz, D_2O) δ 3.80 (s, 1H), 4.24 (d, 1H, $J_{4,3}$ = 3.3 Hz, 1H), 4.48 (d, J = 3.2 Hz, 1H) ; ^{13}C NMR (75 MHz, D_2O) δ 56.9, 71.2, 76.2, 173.9, 178.3.

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17. Neither the ^{1}H nor the ^{13}C NMR of compound **3** showed the presence of a mixture of diastereomers which would result from partial or complete epimerisation of one or more of the three chiral centers. Within the limits of detection of impurities by NMR, compound (*3S,4S*)-**3** can thus be considered to be >95% pure.
18. A preliminary study of the pharmacological activity of (3*S*,4*S*)-**3** with respect to glutamate receptors will be reported elsewhere.