Synthesis of Optically Pure 3,4-Disubstituted L-Glutamates from a Novel 2,3-Aziridino-γ-lactone 4-Carboxylate Derivative

Philippe Dauban, Angèle Chiaroni,[1] Claude Riche,[1] and Robert H. Dodd*

Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91198 Gif-sur-Yvette Cedex, France

Received November 8, 1995[⊗]

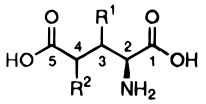
The synthesis of the *N*-acetyl and *N*-Cbz derivatives of (1*S*,4*S*,5*R*)-4-(methoxycarbonyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**24** and **27**, respectively) from D-ribose is described. While compound **24** reacted with methanol in the presence of boron trifluoride etherate to give the novel 2,3-imino-glutamate derivative **28**, compound **27** afforded, under the same conditions, the 4(*S*)-hydroxy-3(*S*)-methoxy-L-glutamate **31**. Similarly, reaction of **27** with ethanol and benzyl alcohol gave the corresponding 3(*S*)-ethoxy and 3(*S*)-(benzyloxy) analogues of **31**. This represents the first example of the use of a carbohydrate for the preparation of L-glutamate derivatives as well as the first example of a stereocontrolled synthesis of glutamate analogues dissymmetrically substituted at the β,γ-positions.

Introduction

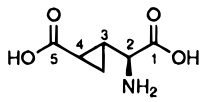
In addition to being a constituent of a myriad of naturally occurring peptides and proteins, L-glutamic acid is the most important excitatory neurotransmitter in the mammalian brain, acting on various subclasses of the glutamate receptor.[2] Moreover, this amino acid is implicated in a wide variety of metabolic processes.[3] For example, L-glutamic acid serves as a precursor in the central nervous system for the inhibitory neurotransmitter γ-aminobutyric acid (GABA) via the action of glutamate decarboxylase while glutamine synthetase transforms glutamic acid into glutamine. It also has a pivotal role in transaminase-catalyzed biosyntheses of other amino acids.

The biological importance of L-glutamic acid has incited a great deal of effort to chemically modify its structure in order to modulate its biological activity. Analogues carrying substituents at either the C-3[4] or the C-4[4dgi,5] positions have been particularly well-studied synthetic targets. In contrast, much less attention has been paid to 3,4-disubstituted derivatives of glutamic acid despite the synthetic challenge and therapeutic potential which these molecules present.

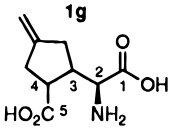
A few examples of 3,4-disubstituted glutamic acid derivatives have been found in nature. Thus, two stereoisomers of 3-hydroxy-4-methyl-L-glutamic acid (**1a**) have been isolated from the seeds of the legume *Gymnocladus dioicius*[6] while the seeds of *Gleditsia caspica*[7] and *Lepidium*[8] are sources of 3-hydroxy-4-methylene- and 3,4-dihydroxy-L-glutamic acid, respectively (**1b** and **1c**).



1a : R^1 = OH ; R^2 = CH_3
1b : R^1 = OH ; R^2 = H_2C=
1c : R^1 = R^2 = OH
1d : R^1 = R^2 = CH_3
1e : R^1 = OH ; R^2 = NH_2
1f : R^1 = *t*-Bu ; R^2 = CO_2H



1g



1h

Nonstereoselective syntheses of the 3,4-dimethyl[9] and 3-hydroxy-4-amino[10] derivatives **1d** and **1e**, respectively,

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1996.

(1) Responsible for the X-ray crystallographic study.

(2) For reviews, see: (a) Kalb, R. G. *Neuroscientist* **1995**, *1*, 60. (b) Bigge, C. F. *Biochem. Pharmacol.* **1993**, *45*, 1547. (c) Nakanishi, S. *Science* **1992**, *258*, 597. (d) Watkins, J. C.; Krogsgaard-Larsen, P.; Honoré, T. *Trends Pharmacol. Sci.* **1990**, *11*, 25. (e) Monaghan, D. T.; Bridges, R. J.; Colman, C. W. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365. (f) Johnson, R. L.; Koerner, J. F. *J. Med. Chem.* **1988**, *31*, 2057.

(3) Gani, D. Pyridoxal Dependent Systems. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, 1990; Vol. 2, Chapter 6.5.

(4) Synthesis and biological activities of 3-substituted glutamic acid derivatives: (a) Jako, I.; Uiber, P.; Mann, A.; Wermuth, C.-G.; Boulanger, T.; Norberg, B.; Evrard, G.; Durant, F. *J. Org. Chem.* **1991**, *56*, 5729. (b) Yanagida, M.; Hashimoto, K.; Ishida, M.; Shinozaki, H.; Shirahama, H. *Tetrahedron Lett.* **1989**, *30*, 3799. (c) Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry* **1994**, *5*, 351. (d) Belokon, Y. N.; Bulychev, A. G.; Ryzhov, M. G.; Vitt, S. V.; Batsanov, A.S.; Struchkov, Y. T.; Bakhmutov, V. I.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1865. (e) El Achqar, A.; Boumzebra, M.; Roumestant, M. L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319. (f) McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chadha, R. *J. Org. Chem.* **1988**, *53*, 1947. (g) Kanemasa, S.; Tatsukawa, A.; Wada, E.; Tsuge, O. *Chem. Lett.* **1989**, 1301. (h) Yamaguchi, M.; Torisu, K.; Minami, T. *Chem. Lett.* **1990**, 377. (i) Schöllkopf, U.; Pettig, D.; Busse, U.; Egert, E.; Dyrbusch, M. *Synthesis* **1986** 737. (j) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352. (k) Hartzoulakis, B.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2525. (l) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855. (m) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866. (n) Dell'Uomo, N.; Di Giovanni, M. C.; Misiti, D.; Zappia, G.; Delle Monache, G. *Liebigs Ann. Chem.* **1994**, 641. (o) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021. (p) Kunieda, T.; Ishizuka, T.; Higuchi, T.; Hirobe, M. *J. Org. Chem.* **1988**, *53*, 3381. (q) Takahata, H.; Takamatsu, T.; Yamazaki, T. *J. Org. Chem.* **1989**, *54*, 4812. (r) Vidal-Cros, A.; Gaudry, M.; Marquet, A. *J. Org. Chem.* **1985**, *50*, 3163. (s) Vidal-Cros, A.; Gaudry, M.; Marquet, A. *J. Org. Chem.* **1989**, *54*, 498. (t) Suzuki, K.; Seebach, D. *Liebigs Ann. Chem.* **1992**, 51.

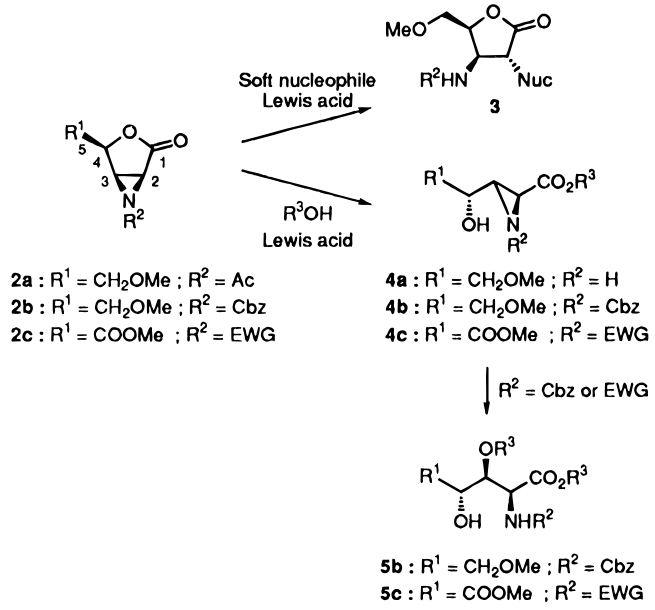
(5) Synthesis of 4-substituted glutamic acid derivatives: (a) Danishefsky, S.; Berman, E.; Clizbe, L. A.; Hirama, M. *J. Am. Chem. Soc.* **1979**, *101*, 4385. (b) Zee-Cheng, R. K. Y.; Olson, R. E. *Biochem. Biophys. Res. Commun.* **1980**, *94*, 1128. (c) Tanaka, K. I.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3879. (d) Attwood, M. R.; Carr, M. G.; Jordan, S. *Tetrahedron Lett.* **1990**, *31*, 283. (e) Baldwin, J. E.; North, M.; Flinn, A.; Moloney, M. G. *Tetrahedron* **1989**, *45*, 1453. (f) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859. (g) Del Bosco, M.; Johnstone, A. N. C.; Bazza, G.; Lopatriello, S.; North, M. *Tetrahedron* **1995**, *51*, 8545. (h) Hanessian, S.; Vanasse, B. *Can. J. Chem.* **1993**, *71*, 1401. (i) Hon, Y. S.; Chang, Y. C.; Gong, M. L. *Heterocycles* **1990**, *31*, 191. (j) Ezquerra, J.; Pedregal, C.; Mico, I.; Najera, C. *Tetrahedron*: *Asymmetry* **1994**, *5*, 921. (k) Baldwin, J. E.; Adlington, R. M.; Robinson, N. G. *J. Chem. Soc., Chem. Commun.* **1987**, 153. (l) Ouerfelli, O.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Synlett* **1993**, 409. (m) Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1993**, *34*, 4667. (n) Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1994**, *35*, 7277. (o) Ezquerra, J.; Pedregal, C.; Yruretagoyena, B.; Rubio, A.; Carreno, M.C.; Escribano, A.; Ruano, J. L. G. *J. Org. Chem.* **1995**, *60*, 2925. (p) Echalier, F.; Constant, O.; Bolte, J. *J. Org. Chem.* **1993**, *58*, 2747. (q) Hudlicky, M.; Merola, J. S. *Tetrahedron Lett.* **1990**, *31*, 7403. (r) Chang, Y. C.; Hon, Y. S.; Chow, W. Y.; Lin, T. A.; Cheng, P. Y.; Wang, C.M. *Brain Res.* **1993**, *604*, 86. (s) Gu, Z. Q.; Hesson, D. P.; Pelletier, J. C.; Maccecchini, M. L.; Zhou, L. M.; Skolnick, P. *J. Med. Chem.* **1995**, *38*, 2518.

(6) (a) Dardenne, G. A.; Casimir, J.; Bell, E. A.; Nulu, J. R. *Phytochemistry* **1972**, *11*, 787. (b) Dardenne, G. A.; Bell, E. A.; Nulu, J. R.; Cone, C. *Phytochemistry* **1972**, *11*, 791.

(7) Dardenne, G.; Casimir, J.; Sorensen, H. *Phytochemistry* **1974**, *13*, 2195.

0022-3263/96/1961-2488$12.00/0

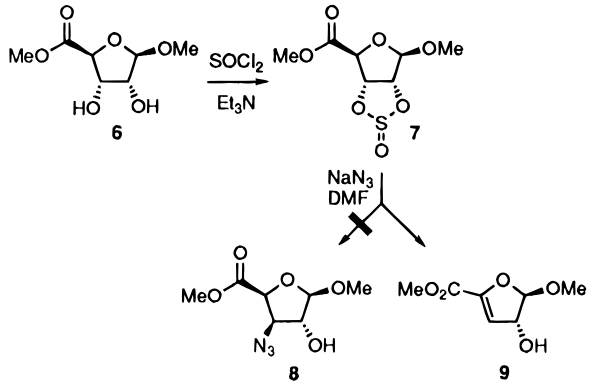
Scheme 1



have been reported. By way of diastereoselective Michael additions of lithium enolates to α,β-unsaturated esters, Kanemasa and co-workers[4g] were able to prepare 3-alkyl-4-carboxy-L-glutamates (e.g., **1f**) having two optically pure chiral centers. Finally, the cyclopropyl-L-glutamic acid derivatives **1g**, found in certain fruits,[11] have been prepared both in their racemic[4h] and stereochemically pure[12] forms. These types of compounds have since been shown to interact selectively with certain subclasses of the glutamate receptor,[13] as has the methylene cyclopentyl derivative **1h**.[14] Both **1g** and **1h** were prepared from α,β-unsaturated esters via cyclopropanation and cycloaddition reactions, respectively.

We have recently reported the synthesis of the 4-(methoxymethyl)-2,3-aziridino-γ-lactone derivatives **2a**,**b** from D-ribose.[15,16] These molecules, which may be considered as cyclic analogues of the synthetically useful aziridine-2-carboxylic esters, were subsequently shown to have a distinctive reactivity pattern with respect to nucleophiles (Scheme 1). In particular, it was observed that, in the presence of a Lewis acid, soft nucleophiles (indole, thiols, halogen, acetate)[16,17] attack the aziridine ring of **2a** and **2b** exclusively at the C-2 position to give lactones of type **3**, in contrast to the reactivity of such nucleophiles with aziridine-2-carboxylic esters, in which the C-3 position is preferentially attacked.[18]

Scheme 2



In the case of hard nucleophiles (e.g., alcohols), the reactivity pattern of the 2,3-aziridino-γ-lactones was observed to also depend on the type of electron-withdrawing group activating the aziridine ring.[16] Thus, the *N*-acetate **2a** gave exclusively aziridine-2-carboxylic esters **4a**, the result of nucleophile-induced lactone ring opening and *N*-deacetylation. In the case of the *N*-Cbz derivative **2b**, however, both the lactone and the aziridine rings were opened by the nucleophile, the latter being effected this time exclusively at the C-3 position, furnishing 3(*S*)-alkoxy-4(*S*)-hydroxy-L-amino acids **5b**. These experimental results were rationalized in terms of HOMO−LUMO theories and MNDO calculations.[16,17]

The ability to synthesize amino acids such as **5b** from aziridino-γ-lactone **2b** suggested to us a convenient pathway to the little known 3,4-disubstituted glutamate class of compounds. As shown in Scheme 1, 3-alkoxy-4-hydroxyglutamates **5c** should be accessible starting from a 2,3-aziridino-γ-lactone carrying a carboxylate function at the C-4 position (i.e., **2c**). In this paper, we report the synthesis of such a compound from D-ribose and its exploitation in the preparation of novel, stereochemically pure, and defined 3,4-disubstituted glutamate derivatives of type **5c**.

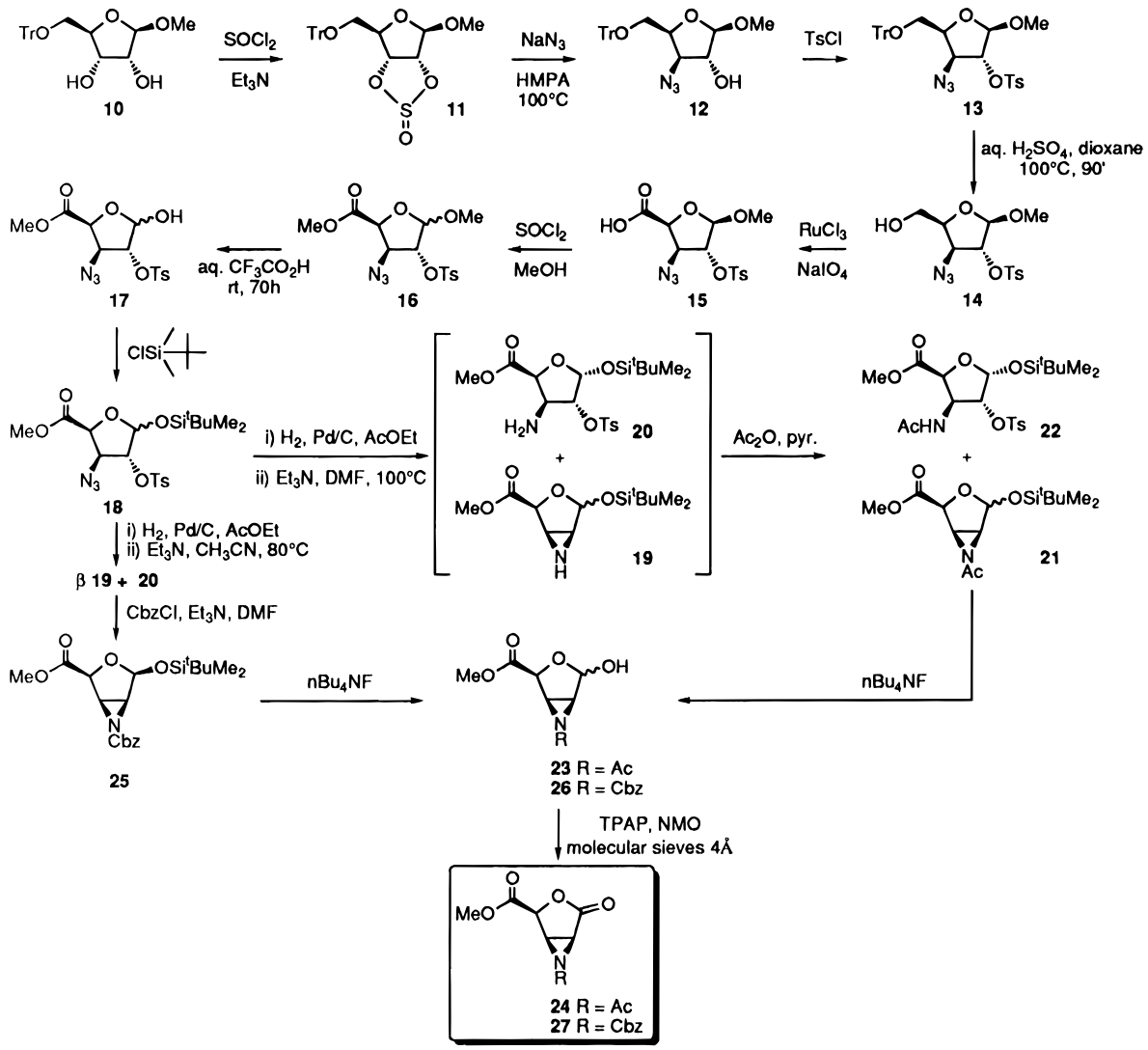
Results and Discussion

Preparation of 4-(Methoxycarbonyl)-2,3-aziridino-γ-lactone Derivatives (24 and 27). In our original preparation of the 4-(methoxymethyl) derivatives **2a**,**b**, the aziridine ring was formed by reductive cyclization of a 3-azido-2-tosylate, the azide function being introduced by nucleophilic attack of the 2,3-*O*-sulfinyl precursor derived from methyl 5-*O*-methylribofuranoside.[15] We thus initially attempted to adapt this route to the synthesis of the desired 4-(methoxycarbonyl) analogue of type **2c** starting from the known methyl uronate **6**.[19] However, as shown in Scheme 2, it was quickly realized that this would not be practicable since treatment of the 2,3-*O*-sulfinyl derivative **7** (prepared by reaction of **6** with thionyl chloride in the presence of triethylamine) with sodium azide in DMF gave the elimination product **9** instead of the expected 3-azido compound **8** due, no doubt, to the increased acidity of the C-4 proton of uronates compared to ordinary ribofuranosides.[20]

Our strategy was thus modified such that the azide group was introduced prior to formation of the 4-carboxylate function. As shown in Scheme 3, the starting

(8) (a) Mueller, A. L.; Uusheima, K. *Acta Chem. Scand.* **1965**, *19*, 1987. (b) Virtanen, A. I.; Ettala, T. *Acta Chem. Scand.* **1957**, *11*, 182.
(9) Liebster, J.; Kopoldova, J.; Babicky, A. *Radiat. Res.* **1963**, *19*, 551.
(10) Alekseeva, L. V.; Burde, N. L.; Podgornaya, I. V.; Ivakin, A. A. *Zh. Obshch. Khim.* **1977**, *47*, 695; *Chem. Abstr.* **1977**, *87*, 38648b.
(11) Fowden, L.; Smith, A.; Millington, D. S.; Sheppard, R. C. *Phytochemistry* **1969**, *8*, 437.
(12) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167.
(13) Ohfune, Y.; Shimamoto, K.; Ishida, M.; Shinozaki, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 15 and references therein.
(14) Raghavan, S.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Tetrahedron Lett.* **1993**, *34*, 5765.
(15) Dubois, L.; Dodd, R. H. *Tetrahedron* **1993**, *49*, 901.
(16) Dauban, P.; Dubois, L.; Tran Huu Dau, E.; Dodd, R. H. *J. Org. Chem.* **1995**, *60*, 2035.
(17) Dubois, L.; Mehta, A.; Tourette, E.; Dodd, R. H. *J. Org. Chem.* **1994**, *59*, 434.
(18) For reviews, see: (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (b) Legters, J.; Willems, J. G. H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59 and references therein.
(19) Jung, K.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1979**, 1426.
(20) Schmidt, R. R.; Heermann, D.; Jung, K.-H. *Liebigs Ann. Chem.* **1974**, 1856.

Scheme 3



material for these transformations was methyl 5-*O*-trityl-*β*-D-ribofuranoside (**10**).[21] Gero and co-workers[22] have described the preparation of the 2,3-di-*O*-tosyl derivative of **10**. However, these authors were not able to displace either of the tosyl groups by azide anion, presumably due to steric hindrance produced by the trityl group. Since the cyclic sulfinyl moiety is generally a better leaving group than tosyl,[23] we chose to prepare the former derivative of **10** by the usual treatment with thionyl chloride and triethylamine. The resulting compound **11**, which is stable and easily purified by chromatography, then reacted smoothly with sodium azide in HMPA at 100 °C to give **12**. Although DMF could also be used as a solvent in this reaction, higher temperatures (145 °C) were necessary, more degradation products were observed, and product yield was 2-fold lower. Nucleophilic attack of azide anion exclusively at the C-3 position of **11** was evident from the ^{1}H NMR spectrum of the product **12** in which the anomeric proton was observed as a singlet, indicative of a *trans* arrangement with H-2. Such complete regioselectivity of attack of carbohydrate cyclic sulfinyl groups by azide anion has previously been observed.[23]

As a prelude to the formation of the aziridine ring and also to protect the C-2 hydroxyl function during the subsequent oxidation of the C-5 position, compound **12** was tosylated to give **13**. The latter, dissolved in a 1:2 mixture of 0.5 M sulfuric acid and dioxane, was selectively hydrolyzed to the 5-hydroxy derivative **14** after 90 min at 100 °C. Oxidation of the free hydroxy group of **14** could then be effected in high yield using conditions described by Sharpless.[24] Thus, treatment of **14** with a catalytic quantity of ruthenium trichloride and excess sodium metaperiodate in a mixture of water, CCl_4, and acetonitrile gave a 91% yield of the carboxylic acid **15**. This compound was transformed into its methyl ester **16** by the action of thionyl chloride in methanol. The IR spectrum of **16** showed the expected absorptions corresponding to azide, sulfonyl, and ester functions, while the ^{1}H NMR spectrum revealed the presence of the three methyl groups belonging to the ether, ester, and tosyl functionalities. The two-singlet nature of each of these signals indicated that anomerization (β:α = 3:2) had occurred during the esterification step. However, since

(21) Kawana, M.; Kuzuhara, H.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1492.
(22) Cleophax, J.; Gero, S. D.; Hildesheim, J.; Sepulchre, A. M.; Guthrie, R. D.; Smith, C. W. *J. Chem. Soc. C* **1970**, 1385.
(23) Guiller, A.; Gagnieu, C. H.; Pacheco, H. *Tetrahedron Lett.* **1985**, *26*, 6343.
(24) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

a γ-lactone structure was our ultimate goal, this isomerization was not considered an impediment and no effort was made to separate the anomers.

Before we proceeded with aziridine ring formation, the anomeric methyl ether of **16** was transformed into the *tert*-butyldimethylsilyl ether **18**. This exchange of anomeric blocking groups is necessary at this point since, unlike the methyl ether, the silylated derivative can be deprotected (i.e., by fluoride ion) in the presence of the sensitive aziridine ring. Thus, hydrolysis of **16** with aqueous trifluoroacetic acid (conditions being carefully optimized to avoid concomitant hydrolysis of the ester function)[25] followed by treatment of the product **17** with *tert*-butyldimethylsilyl chloride and imidazole in DMF[26] afforded **18** in approximately 70% overall yield.

Formation of the 2,3-aziridine ring was then studied. In the 4-(methoxymethyl) series (**2a**,**b**), the aziridine ring was obtained by a modified Staudinger reaction, that is, treatment of the corresponding 3-azido-2-tosylate with triphenylphosphine followed by hydrolysis of the intermediate triphenylphosphinimine with hot aqueous sodium hydroxide.[15,27] The presence of the ester function in **18**, however, clearly precluded use of this methodology. Hashimoto and co-workers[28] have reported the formation of an aziridine ring from a 2-azido-3-mesylpyranose derivative by way of catalytic hydrogenation (palladium on carbon) of the azide followed by base-promoted cyclization (sodium acetate in aqueous DMF at 90 °C). Applied to compound **18**, these conditions effectively produced the desired aziridine **19**, but in only mediocre yields. Much better results were obtained when sodium acetate was replaced by triethylamine in the cyclization step and the presence of water was eliminated. In this case, **19**, characterized as its *N*-acetyl derivative **21** after treatment of the crude reaction product with acetic anhydride in pyridine, was obtained in 70% yield. A second minor product (15%) formed with **21** after the sequence hydrogenation/base treatment/acetylation, was shown to be the uncyclized acetamide **22**. Interestingly, though the starting material **18** and the major product **21** of this series of reactions were α,β anomeric mixtures, compound **22** was observed by ^{1}H NMR spectroscopy to be composed exclusively of the α-anomer on the basis of the H1−H2 coupling constant of 3.5 Hz. This suggested that the α-anomer of the intermediate 3-amino-2-tosylate (**20**) cyclizes less readily than its β-anomer. This was conclusively demonstrated by running the cyclization reaction in refluxing acetonitrile instead of in DMF at 100 °C. In this case, only the β-anomer of the intermediate amine cyclized to give pure (β)-aziridine **21** in 55% yield after acetylation, the α-anomer leading entirely to the uncyclized compound **22** in 30% yield.[29]

Preparation of the desired lactone from **21** then proceeded uneventfully. Thus, treatment of **21** with tetrabutylammonium fluoride in dichloromethane afforded the aziridino furanose **23** in good yield. Oxidation of the free hydroxyl group of the latter with catalytic tetrapropylammonium perruthenate (TPAP)[30] in the presence of 4-methylmorpholine *N*-oxide (NMO) then gave the 2,3-aziridino-γ-lactone **24**, a stable, crystalline solid.

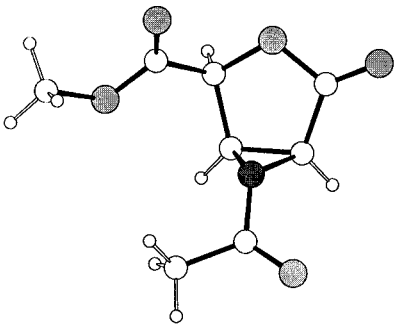


Figure 1. X-ray crystal structure of compound **24**.

Since, as discussed above, the *N*-Cbz (**2b**) and the *N*-acetyl (**2a**) 4-(methoxymethyl) derivatives were shown to have different reactivity patterns toward nucleophiles,[16] the *N*-Cbz analogue of ester **24** was also prepared. Aziridine **19** was thus treated with benzyl chloroformate, DMAP, and triethylamine in DMF, giving the *N*-Cbz furanoside **25**[31] which was transformed into lactone **27** after sequential treatment with fluoride anion and TPAP/NMO.

The structural identities of both key compounds **24** and **27** were fully consistent with the spectroscopic and analytical data. In particular, both compounds showed three carbonyl absorptions in the infrared spectrum, one of which, in the 1800 cm^{-1} region, is characteristic of the lactone structure. Moreover, in the ^{1}H NMR spectra, the bridging protons H-2 and H-3 are shifted downfield in going from the lactols (3.2−3.5 and 3.5−3.7 ppm, respectively) to the lactones (3.6−4.0 ppm).[32] Finally, the structure of the *N*-acetylaziridino-γ-lactone **24** was confirmed by X-ray crystallography (Figure 1).[33]

Reactivity of 24 and 27 toward Alcohols:Preparation of 3,4-Disubstituted Glutamate Derivatives. We have previously shown[16] that the 4-(methoxymethyl)-*N*-acetyl-2,3-aziridino-γ-lactone **2a** reacts with hard nucleophiles such as methanol in the presence of a Lewis acid catalyst (boron trifluoride etherate) to give exclusively the product arising from lactone ring opening by the nucleophile and *N*-deacetylation (i.e., **4a**, R^3 = CH$_3$). The latter process deactivates the aziridine ring, protecting it from further nucleophilic attack. The reactivity

(25) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1989**, *30*, 6503.

(26) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(27) Pinter, I.; Kovacs, J.; Messmer, A.; Kalman, A.; Toth, G.; Lindberg, B. K. *Carbohydr. Res.* **1979**, *72*, 289.

(28) Araki, K.; Kawa, M.; Saito, Y.; Hashimoto, H.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3137.

(29) As pointed out by a reviewer, the relative proportion of β- to α-anomer decreases in transforming **17** (β:α = 2:1) into the reaction products **21** and **22** (β-**21**:α-**21** + α-**22** = 1:1). Because none of the reaction conditions used for this transformation is likely to cause anomerization in favor of the α-anomer, it is more probable that the *apparent* enrichment in α-anomer may be due to the greater chemical instability of β-**21** (or its precursor β-**19**) compared to α-**21** and α-**22** under the conditions of the cyclization reaction (DMF and triethylamine at 100 °C). Thus, when milder conditions are used (acetonitrile and triethylamine at 82 °C), the β:α ratio of the final products remains 2:1, as in the starting material.

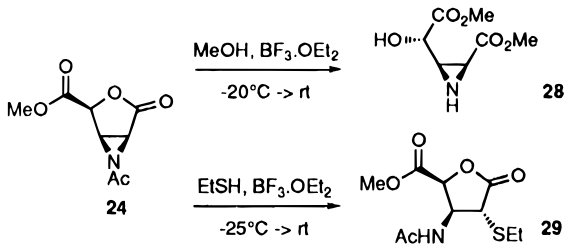
(30) For a review, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(31) The starting material **19** used for the synthesis of **25** was prepared from **18** using acetonitrile rather than DMF during the cyclization step in order to provide exclusively the β-anomer (together with uncyclized α-**20**). The small proportion (<10%) of α-**25** formed during Cbz-chloride treatment of the mixture of β-**19** and **20** is probably the result of the use of DMF and triethylamine in this step, conditions observed to promote cyclization of **20** to α-**19**.

(32) For simplicity of discussion, carbohydrate ring numbering (i.e., as in Scheme 1) has been used throughout for all compounds despite the fact that the ring atoms of some of these compounds (e.g., **24**, **27**, **29**, **32**, **34**) are numbered differently in the official IUPAC nomenclature (see Experimental Section).

(33) The authors have deposited atomic coordinates for compound **24** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK.

Scheme 4



pattern of the 4-(methoxycarbonyl) analogue **24** proved to be identical (Scheme 4), reaction with methanol at 20 °C in the presence of 2 equiv of boron trifluoride etherate producing the novel dimethyl iminoglutamate derivative **28**. The IR spectrum of **28** showed only one carbonyl (ester) band, while in the ^{1}H NMR spectrum the H-2 and H-3 signals of the aziridine ring were shifted to high field (2.86 and 2.52 ppm, respectively) and the *N*-acetyl signal was no longer visible.

With respect to soft nucleophiles, the reactivity of ester **24** also paralleled that of the methoxy derivative **2a**[16] since, in the presence of ethanethiol, only compound **29**, the product of nucleophilic attack of the aziridine ring at C-2, was observed. This regioselectivity is evident from the ^{1}H NMR spectrum of **29** in which H-2 is observed as a doublet, *trans* to H-3 (J = 5.8 Hz), itself coupled to three protons (NH, H-2, H-4).

In view of these results, it seemed reasonable to assume that the *N*-Cbz-aziridino-γ-lactone **27** would behave in the same manner toward methanol as its 4-(methoxymethyl) analogue **2b**. In the latter case, the *N*-Cbz blocking group was found to be stable under the conditions of the reaction (2 equiv of Lewis acid, 20 °C),[16] thus allowing opening of both the lactone ring and the aziridine ring (at C-3) to give a 3-methoxy-4-hydroxy α-amino acid derivative (i.e., **5b**, $R^3 = CH_3$). Surprisingly, however, the crude product obtained from the reaction of the 4-(methoxycarbonyl)-*N*-Cbz derivative **27** with methanol under identical conditions yielded only the product of lactone ring opening **30** (Scheme 5), the aziridine ring having resisted nucleophilic attack despite the presence of the activating *N*-Cbz group. By heating the reaction mixture at 50 °C for 90 min, aziridine ring opening could be achieved, affording in good yield (60%) the 3(*S*)-methoxy-4(*S*)-hydroxy-L-glutamate derivative **31**. This represents the first example of a stereocontrolled preparation of a 3,4-disubstituted glutamate as well as the first example of the use of a carbohydrate (D-ribose) for the synthesis of an L-glutamic acid derivative.[34]

Compound **31** underwent partial cyclization to the lactone form **32** during the course of its purification on silica gel. The formation of this compound from **31** confirmed the structure and stereochemistry of the latter since the ^{1}H NMR data for **32** were consistent with the introduction of the methoxy group at C-3 of the lactone, *trans* to both substituents at C-2 and C-4 (i.e., via an S_N2 pathway).[32] Thus, H-2 and H-3 were observed as doublets of doublets with a coupling constant of 5.5 Hz while the H3−H4 coupling constant was 4.5 Hz.

A ^{1}H NMR spectrum of the crude product obtained when aziridino-γ-lactone **27** was reacted with ethanol at 70 °C for 3 h in the presence of 2 equiv of boron trifluoride etherate showed that, as with methanol, both lactone ring opening and aziridine ring opening had occurred. However, partial transesterification of the 4-(methoxycarbonyl) group to a 4-(ethoxycarbonyl) group (∼15%) was also evident. In view of this, the reaction time was extended to 45 h, thereby allowing complete conversion of **27** into the diethyl 3-ethoxy-4-hydroxy-L-glutamate derivative **33**. Partial cyclization of **33** to the lactone **34** was again observed during the course of its purification on silica gel.

Finally, the reaction of benzyl alcohol with **27** was studied. By use of only 1 equiv of boron trifluoride etherate and by heating the reaction mixture for only 2 h, lactone and aziridine ring opening could be selectively achieved while transesterification of the methyl ester was completely suppressed. Relactonization of this product (**35**) could in turn be prevented by acetylation of its free hydroxyl group (**36**). Alternatively, when the reaction of **27** with benzyl alcohol was run at room temperature, only the product of lactone ring opening (**37**) was obtained. The presence of a hydroxyl group in **37** was evident from both the IR and ^{1}H NMR spectra of the compound, relactonization apparently being prevented by the rigidity imparted by the intact aziridine ring.

Compound **37**, an aziridine-2-carboxylate, is a potentially valuable intermediate for the preparation of hitherto unknown 3,4-disubstituted glutamate derivatives in view of the general observation that this class of compounds reacts with all types of nucleophiles (hard or soft) practically always at the C-3 position to give α-amino acids.[18,35] In contrast, the distinctive feature of the 2,3-aziridino-γ-lactones is, as we have described here and elsewhere, their propensity to react selectively with nucleophiles at the C-2 or C-3 positions depending on whether these nucleophiles are, respectively, soft or hard. Inasmuch as an aziridino-γ-lactone such as **27** allows either direct access to 3,4-disubstituted glutamates (e.g., **31**, **33**, **35**) or to an intermediate **37** in turn susceptible to conversion to such compounds, the methodology reported here may be considered to be the only one available at present for the stereocontrolled synthesis of 3,4-disubstituted L-glutamates. We are currently exploring the use of **27** and **37** for this purpose, as well as investigating the biological properties which these novel molecules may possess.

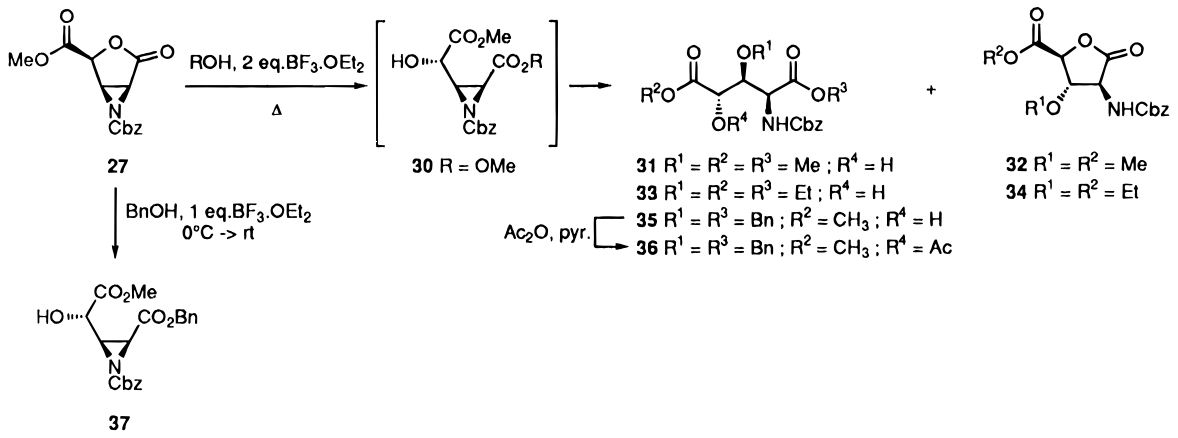
Experimental Section

General. Melting points are uncorrected. IR spectra of samples were obtained as films (i.e., by application of a $CHCl_3$ solution to an NaCl plate followed by evaporation of the solvent). ^{1}H NMR and ^{13}C NMR chemical shifts are given as δ values with reference to Me_4Si as internal standard. TLC and preparative chromatography were performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with UV light (254 nm) and, for TLC, with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230−240 mesh) at medium pressure (200 mbar). All solvents were distilled and stored over 4 Å molecular sieves before use. Boron trifluoride etherate, TPAP, 4-methylmorpholine *N*-oxide, and benzyl chloroformate were purchased from Aldrich Chemical Co. and were used without further purification.

(34) For a review of the use of carbohydrates for the stereocontrolled synthesis of amino acids, see: Cintas, P. *Tetrahedron* **1991**, *47*, 6079.

(35) We have confirmed that compound **37** reacts with nucleophiles in the same manner as the classical aziridine 2-carboxylic esters. Thus, for example, ethanethiol attacks **37** exclusively at the C-3 position to give the corresponding 3-(ethylthio)-4-hydroxy-L-glutamate derivative. The preparation of a variety of disubstituted glutamates from **37** will be the subject of a separate report.

Scheme 5



Element analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

Methyl (Methyl 2,3-*O*-Sulfinyl-*β*-D-ribofuranosid)uronate (7). To a solution of the diol **6** (41 mg, 0.21 mmol) and triethylamine (0.12 mL, 0.84 mmol) in THF (2 mL) was added at −25 °C under nitrogen freshly distilled thionyl chloride (30 μL, 0.42 mmol). The reaction mixture was stirred for 15 min at −25 °C and diluted with ethyl acetate (5 mL) before addition of saturated aqueous NaCl solution (5 mL). The organic phase was separated, washed with aqueous NaCl solution (2 × 5 mL), and dried over Na_2SO_4. Removal of the solvents under reduced pressure left a yellow oil which was purified by passing through a pad of silica gel (dichloromethane−ethanol 98:2). Compound **7** (48 mg, 95%), an oil, was thus obtained as a 1:1 mixture of *exo* and *endo* isomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.40 (s, 1.5 H), 3.41 (s, 1.5 H), 3.79 (s, 3H), 4.70 (s, 0.5 H), 4.96 (s, 0.5 H), 5.00 (d, 0.5 H, $J_{2,3}$ = 6.5 Hz), 5.14 (s, 0.5 H), 5.25 (d, 0.5 H, $J_{2,3}$ = 5.9 Hz), 5.31 (s, 0.5 H), 5.80 (d, 0.5 H), 5.99 (d, 0.5 H); IR (film) 1738, 1450, 1212 cm^{-1}; mass spectrum (CI) *m/z* 239 $(MH)^+$. Anal. Calcd for $C_7H_{10}O_7S$: C, 35.29; H, 4.23; O, 47.02; S, 13.46. Found: C, 35.60; H, 4.07; O, 47.38; S, 13.32.

Methyl (4*R*,5*R*)-4,5-Dihydro-4-hydroxy-5-methoxy-2-furancarboxylate (9). A solution of compound **7** (48 mg, 0.2 mmol) in DMF (2 mL) was heated for 1 h at 100 °C in the presence of sodium azide (39 mg, 0.6 mmol). *(Caution! Hazardous chemical.)* The solvent was then removed *in vacuo*, the residue was taken up in ethyl acetate (5 mL), and the solution was washed with saturated aqueous NaCl solution (2 × 5 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using CH_2Cl_2−ethanol (95:5) as eluent. Compound **9** was obtained as a colorless oil in 70% yield (25 mg): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.50 (m, 1H, exchangeable with D_2O), 3.54 (s, 3H), 3.85 (s, 3H), 4.71 (m, 1H), 5.28 (d, 1H, $J_{5,4}$ = 1.0 Hz), 6.03 (d, 1H, $J_{3,4}$ = 2.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.7, 59.3, 78.6, 111.6, 113.1, 149.9, 171.3; IR (film) 3425, 1734, 1631 cm^{-1}; mass spectrum (CI) *m/z* 175 $(MH)^+$, 157 $(MH - H_2O)^+$. Anal. Calcd for $C_7H_{10}O_5 \cdot 1/4H_2O$: C, 47.06; H, 5.92; O, 47.02. Found: C, 47.44; H, 5.92; O, 47.32.

Methyl 2,3-*O*-Sulfinyl-5-*O*-(triphenylmethyl)-*β*-D-ribofuranoside (11). To a solution of diol **10** (11.5 g, 28.3 mmol) and triethylamine (16 mL, 113 mmol) in anhydrous THF (150 mL) held at −25 °C was added dropwise over 45 min a solution of freshly distilled thionyl chloride (4.1 mL, 56.6 mmol) in THF (10 mL). The reaction mixture was stirred for a further 45 min at −25 °C. At the end of the reaction period, ethyl acetate (150 mL) was added followed by saturated aqueous NaCl solution (200 mL). The aqueous layer was separated, and the organic phase was washed with NaCl solution (2 × 100 mL). The organic phase was dried (Na_2SO_4), the solvents were removed under reduced pressure, and the oily residue was purified by column chromatography on silica gel (heptane−ethyl acetate 4:1), yielding compound **11** (11.0 g, 86%) as a faintly colored solid: mp 101−102 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.20 (s, 1.5 H, *endo* (or *exo*) isomer), 3.23 (s, 1.5H, *exo* (or *endo*) isomer), 3.10−3.50 (m, 2H), 4.37 (dd, 0.5 H, $J_{4,3}$ = 0.8 Hz, $J_{4,5}$ = 6.3 Hz), 4.69 (dd, 0.5H, $J_{4,3}$ = 1.3 Hz, $J_{4,5}$ = 5.7 Hz), 4.93 (d, 0.5 Hz, $J_{2,3}$ = 6.5 Hz), 5.00 (s, 0.5H), 5.13 (dd, 0.5H), 5.17 (d, 0.5H), 5.25 (s, 0.5H), 5.37 (d, 0.5H), 7.15−7.50 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.2, 55.3, 64.0, 64.3, 84.6, 85.4, 86.1, 87.3, 87.7, 88.9, 90.9, 108.2, 108.7, 127.4, 128.1, 128.7, 143.7; IR (film) 1215 cm^{-1}; mass spectrum (CI) *m/z* 452 $(M)^+$. Anal. Calcd for $C_{25}H_{24}O_6S$: C, 66.35; H, 5.35; O, 21.22; S, 7.08. Found: C, 66.53; H, 5.42; O, 21.14; S, 7.14.

Methyl 3-Azido-3-deoxy-5-*O*-(triphenylmethyl)-*β*-D-xylofuranoside (12). A solution of compound **11** (11.6 g, 25.6 mmol) in anhydrous HMPA (120 mL) *(Warning! Toxic solvent)* was heated at 100 °C for 15 h in the presence of sodium azide (5.0 g, 76.9 mmol). *(Caution! Hazardous chemical.)* The solvent was then removed *in vacuo*, and the crude reaction product was taken up in ethyl acetate (200 mL). The solution was washed with water (3 × 150 mL), the organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The oily residue was purified by column chromatography on silica gel. Elution of the column with 3:1 heptane−ethyl acetate resulted in isolation of unreacted **11** (1.0 g, 9%). Further elution with 2:1 heptane−ethyl acetate afforded compound **12** as a colorless oil (8.8 g, 80%): $[\alpha]^{22}_D$ −51.5° (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.46 (m, 1H, exchangeable with D_2O), 3.28 (dd, 1H, $J_{5,4}$ = 5.5 Hz, $J_{5,5'}$ = 9.7 Hz), 3.35 (s, 3H), 3.40 (dd, 1H, $J_{5',4}$ = 6.3 Hz), 3.96 (dd, 1H, $J_{3,2}$ = 2.4 Hz, $J_{3,4}$ = 5.7 Hz), 4.24 (m, 1H), 4.50 (pseudo q, 1H, $J_{4,5}$ = 5.8 Hz), 4.82 (s, 1H), 7.15−7.50 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.8, 63.4, 66.9, 79.9, 80.0, 87.3, 109.5, 127.2, 127.9, 128.9, 144.0; IR (film) 3415, 2106 cm^{-1}; mass spectrum (EI) *m/z* 431 $(M)^+$. Anal. Calcd for $C_{25}H_{25}N_3O_4$: C, 69.59; H, 5.84; O, 14.83; N, 9.74. Found: C, 69.57; H, 5.87; O, 15.01; N, 9.73.

Methyl 3-Azido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-5-*O*-(triphenylmethyl)-*β*-D-xylofuranoside (13). A solution of compound **12** (11.5 g, 26.7 mmol) in pyridine (200 mL) was treated at 0 °C with *p*-toluenesulfonyl chloride (15.2 g, 80.0 mmol), and the reaction mixture was stirred for 72 h at rt. The solvent was then removed under reduced pressure, and the solid residue was partitioned between ethyl acetate (300 mL) and water (300 mL). The phases were separated, and the organic phase was dried over Na_2SO_4. Removal of the solvent *in vacuo* left a yellow oil which was purified by column chromatography on silica gel (heptane−ethyl acetate 9:1 followed by 8:1), affording **13** (14.0 g, 90%) as a colorless oil: $[\alpha]^{22}_D$ −27.9° (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.23 (s, 3H), 3.24 (dd, 1H, $J_{5,4}$ = 6.0 Hz, $J_{5,5'}$ = 9.7 Hz), 3.38 (dd, 1H), 4.08 (d, 1H, $J_{3,4}$ = 5.8 Hz), 4.41 (pseudo q, 1H), 4.74 (s, 1H), 4.82 (s, 1H), 7.23−7.46 (m, 17H), 7.82 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.5, 55.9, 62.9, 64.9, 80.0, 86.0, 87.3, 106.8, 127.1, 127.8, 128.2, 128.7, 130.2, 133.0, 143.8, 145.8; IR (film) 2110, 1180 cm^{-1}; mass spectrum (EI) *m/z* 585 $(M)^+$. Anal. Calcd for $C_{32}H_{31}N_3O_6S$: C, 65.62; H, 5.34; O, 16.39; N, 7.17; S, 5.47. Found: C, 65.70; H, 5.59; O, 15.99; N, 6.80; S, 5.27.

Methyl 3-Azido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-*β*-D-xylofuranoside (14). A solution of compound **13** (4.6 g, 7.85 mmol) and sulfuric acid (20 mL of a 0.5 M solution) in dioxane (40 mL) was heated at 100 °C for 90 min. The reaction mixture was then cooled to rt, diluted with saturated aqueous NaCl solution (25 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), the solvents were evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (heptane−ethyl acetate 2:1 followed by 1:1), affording compound **14** (2.3 g, 85%) as a colorless oil: $[\alpha]^{22}_D$ −78.8° (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.34 (s, 3H), 3.70 (m, 2H), 4.21 (dd, 1H, $J_{3,2}$ = 4.4 Hz, $J_{3,4}$ = 7.2 Hz), 4.35 (dt, 1H, $J_{4,5}$ = 7.8 Hz), 4.81 (dd, 1H, $J_{2,1}$ = 1.5 Hz), 4.91 (d, 1H), 7.39 (d, 2H, J = 8.2 Hz), 7.83 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 56.1, 61.8, 65.0, 81.0, 86.7, 106.9, 128.2, 130.2, 132.7, 145.8; IR (film) 3400, 2110, 1178 cm^{-1}; mass spectrum (EI) *m*/*z* 312 (M − OCH_3)$^+$. Anal. Calcd for $C_{13}H_{17}N_3O_6S$: C, 45.47; H, 4.99; N, 12.24; S, 9.34. Found: C, 45.85; H, 4.94; N, 12.12; S, 9.23.

Methyl 3-Azido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-*β*-D-xylofuranosiduronic Acid (15). A biphasic mixture of water (75 mL), CCl_4 (50 mL) *(Warning! Toxic solvent)*, and acetonitrile (50 mL) containing compound **14** (8.6 g, 25.0 mmol), ruthenium trichloride hydrate (260 mg, 1.25 mmol), and sodium metaperiodate (22.0 g, 102.5 mmol) was stirred vigorously for 4.5 h at rt. The reaction mixture was then diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4), the solvents were removed under reduced pressure, and the dark green oily residue was triturated with diethyl ether in order to precipitate the ruthenium salts. The latter were removed by filtration of the mixture through Celite. The filtrate was concentrated *in vacuo*, leaving compound **15** (8.13 g, 91%) as a lightly colored oil which was used in the following reactions without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.43 (s, 3H), 4.35 (d, 1H, $J_{3,4}$ = 6.4 Hz), 4.80 (s, 1H), 4.95 (d, 1H), 4.99 (s, 1H), 7.42 (d, 2H, J = 8.2 Hz), 7.84 (d, 2H), 8.56 (m, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.8, 56.2, 65.1, 80.0, 84.6, 107.7, 128.2, 130.5, 132.5, 146.3, 172.2; IR (film) 3300, 2125, 1747, 1170 cm^{-1}; mass spectrum (CI) *m*/*z* 358 (MH)$^+$.

Methyl [Methyl 3-azido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-α,*β*-D-xylofuranosid]uronate (16). To a solution of compound **15** (8.13 g, 22.8 mmol) in anhydrous methanol (50 mL) held at −20 °C was added thionyl chloride (3.3 mL, 45.5 mmol) dropwise. After completion of the addition, the reaction mixture was allowed to stir for 20 h at rt and the solvent and excess reagent were removed under reduced pressure. The crude material remaining was purified by column chromatography on silica gel (heptane−ethyl acetate 7:3), affording compound **16** (7.5 g, 89%), an oil, as an inseparable mixture of α and *β* anomers (2:3, respectively): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.46, 2.48 (2 × s, 3H, α and *β* anomer), 3.34 (s, 1.2H, α anomer), 3.43 (s, 1.8H, *β* anomer), 3.79, 3.80 (2 × s, 3H), 4.34 (d, 0.6H, $J_{3,4}$ = 6.5 Hz), 4.50 (dd, 0.4H, $J_{3,4}$ = 7.9 Hz, $J_{3,2}$ = 7.3 Hz), 4.62 (dd, 0.4H, $J_{2,1}$ = 4.2 Hz, $J_{2,3}$ = 7.3 Hz), 4.75 (d, 0.4H), 4.77 (d, 0.6H, $J_{2,1}$ = 0.8 Hz), 4.93 (d, 0.6H), 4.95 (s, 0.6H), 4.98 (d, 0.4H), 7.41 (d, 2H, J = 8.2 Hz), 7.83 (d, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.7, 52.4, 52.5, 55.8, 55.9, 63.5, 65.2, 75.1, 80.0, 80.4, 84.8, 100.7, 107.3, 128.1, 128.2, 130.0, 130.4, 132.5, 145.6, 168.3, 168.4; IR (film) 2120, 1765, 1181 cm^{-1}; mass spectrum (CI) *m*/*z* 372 (MH)$^+$. Anal. Calcd for $C_{14}H_{17}N_3O_7S \cdot 0.04C_7H_{16}$: C, 45.69; H, 4.74; N, 11.19; S, 8.54. Found: C, 45.70; H, 4.81; N, 11.10; S, 8.64.

Methyl 3-Azido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-α,*β*-D-xylofuranuronate (17). A solution of compound **16** (7.6 g, 20.5 mmol) in trifluoroacetic acid and water (120 mL of a 9:1 mixture) was stirred at rt for 70 h. The reaction mixture was then concentrated under reduced pressure at rt, saturated aqueous $NaHCO_3$ (50 mL) was added, and the mixture was extracted with ethyl acetate (2 × 150 mL). The combined organic extracts were dried (Na_2SO_4), affording, after removal of solvents *in vacuo*, compound **17** (5.5 g, 75%) as a lightly colored oil (a 1:2 mixture of α and *β* anomer, respectively) which could be used without further purification in the following step. An analytical sample was obtained by column chromatography of this crude product on silica gel using heptane−ethyl acetate (6:4) as eluent: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.80 (s, 1H, α anomer), 3.84 (s, 2H, *β* anomer), 4.52 (dd, 0.6 H, $J_{3,2}$ = 2.0 Hz, $J_{3,4}$ = 6.9 Hz), 4.53 (dd, 0.4H, $J_{3,2}$ = 5.6 Hz, $J_{3,4}$ = 7.2 Hz), 4.65 (dd, 0.4H, $J_{2,1}$ = 3.9 Hz), 4.76 (d, 0.6H), 4.87 (d, 0.4H), 4.93 (d, 0.6H), 5.29 (s, 0.6H), 5.60 (d, 0.4H), 7.40 (d, 2H, J = 8.0 Hz), 7.83 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 52.5, 52.9, 63.8, 65.4, 75.5, 79.9, 80.7, 85.8, 95.0, 101.7, 128.1, 128.2, 130.2, 130.4, 132.3, 145.9, 146.1, 168.8, 170.1; IR (film) 3460, 2118, 1750, 1181 cm^{-1}; mass spectrum (CI) *m*/*z* 358 (MH)$^+$. Anal. Calcd for $C_{13}H_{15}N_3O_7S$: C, 43.70; H, 4.23; N, 11.76; S, 8.97. Found: C, 43.54; H, 4.16; N, 11.61; S, 8.91.

Methyl [*tert*-Butyldimethylsilyl 3-azido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-α,*β*-D-xylofuranosid]uronate (18). To a solution of compound **17** (5.5 g, 15.4 mmol) in anhydrous DMF were successively added imidazole (2.8 g, 30.8 mmol) and *tert*-butyldimethylsilyl chloride (4.6 g, 23.1 mmol). The reaction mixture was stirred for 20 h at rt, and it was then evaporated to dryness under reduced pressure. The residue was taken up in ethyl acetate (250 mL), and the mixture was washed with water (200 mL). Drying of the organic phase over Na_2SO_4, removal of the solvent *in vacuo*, and purification of the crude product by column chromatography on silica gel (heptane−ethyl acetate 4:1 followed by 3:1) afforded compound **18** (6.6 g, 90%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.00−0.13 (4 × s, 6H), 0.83 (s, 5.4H, *β* anomer), 0.90 (s, 3.6 H, α anomer), 2.46 (s, 1.2H), 2.48 (s, 1.8H), 3.78 (s, 3H), 4.26 (d, 0.6H, $J_{3,4}$ = 5.8 Hz), 4.51 (d, 0.4H, $J_{3,4}$ = 5.4 Hz), 4.52 (d, 0.4H, $J_{2,1}$ = 2.8 Hz), 4.67 (s, 0.6H), 4.79 (m, 1H), 5.29 (s, 0.6H), 5.50 (d, 0.4H), 7.40 (d, 2H, J = 8.0 Hz), 7.83 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, −4.7, 17.8, 17.9, 21.7, 25.4, 25.5, 52.2, 52.5, 63.1, 64.7, 75.0, 79.7, 81.2, 86.1, 94.9, 101.6, 127.6, 128.0, 130.1, 130.3, 132.5, 132.7, 145.6, 146.0, 167.9, 168.7; IR (film) 2120, 1775, 1177 cm^{-1}; mass spectrum (CI) *m*/*z* 472 (MH)$^+$. Anal. Calcd for $C_{19}H_{29}N_3O_7SSi$: C, 48.39; H, 6.20; N, 8.91; S, 6.80. Found: C, 48.39; H, 5.98; N, 8.93; S, 6.81.

Methyl (*tert*-Butyldimethylsilyl 2,3-aziridino-2,3-dideoxy-α,*β*-D-lyxofuranosid)uronate (19) and Methyl [*tert*-Butyldimethylsilyl 3-amino-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-α,*β*-D-xylofuranosid]uronate (20). A solution of compound **18** (2.81 g, 5.96 mmol) in ethyl acetate (60 mL) was hydrogenated at atmospheric pressure for 3 h in the presence of 10% palladium on carbon (260 mg). The reaction was then filtered through Celite, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in DMF (30 mL), triethylamine (8 mL) was added to the solution, and the latter was heated at 100 °C for 6 h. Removal of the solvents under reduced pressure at the end of the reaction period left a brown oil composed of aziridine **19** and uncyclized amine **20** (4:1 respectively, by NMR). This mixture was subjected to the next step without further purification. An analytical sample of **19** was obtained by chromatography of part of the mixture on silica gel using heptane−ethyl acetate (1:1) as eluent: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.13, 0.15, 0.16 (3 × s, 6H), 0.90, 0.92 (2 × s, 9H), 2.65 (d, 0.4H, $J_{2,3}$ = 4.0 Hz, α anomer), 2.72 (d, 0.6H, $J_{2,3}$ = 3.4 Hz, *β* anomer), 2.86 (dd, 0.6H, $J_{3,4}$ = 2.0 Hz), 2.97 (dd, 0.4H, $J_{3,4}$ = 1.8 Hz), 3.79, 3.81 (2 × s, 3H), 4.43 (d, 0.6H), 4.63 (d, 0.4H), 5.46 (s, 0.4H), 5.50 (d, 0.6H, $J_{1,2}$ = 0.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.3, 17.9, 18.0, 25.6, 25.7, 35.5, 36.6, 38.5, 39.4, 52.3, 52.5, 74.8, 74.9, 98.3, 98.4, 169.5, 169.9; IR (film) 3285, 1760 cm^{-1}; mass spectrum (HRCI) calcd for $C_{12}H_{24}NO_4Si$ (MH)$^+$ *m*/*z* 274.1475, found 274.1469.

The amine **20** was characterized as its acetamide derivative **22**, prepared as described below.

Methyl (*tert*-Butyldimethylsilyl *N*-acetyl-2,3-aziridino-2,3-dideoxy-α,*β*-D-lyxofuranosid)uronate (21) and Methyl [*tert*-Butyldimethylsilyl 3-acetamido-3-deoxy-2-*O*-(*p*-tolylsulfonyl)-α-D-xylofuranosid]uronate (22). The 4:1 mixture of **19** and **20** obtained in the preceding experiment was dissolved in pyridine (35 mL), the solution was cooled to 0 °C, and acetic anhydride (6 mL) was added. The reaction mixture was stirred for 24 h at 5 °C after which the solvents were removed under reduced pressure. Chromatography of the

residue on silica gel (heptane−ethyl acetate 2:1) afforded aziridine **21** (1.3 g, 70% based on **18**) as a mixture of α and β anomers (2:3, respectively). Careful preparative TLC using the same eluents allowed isolation of pure β-**21** as a white solid: mp 108−109 °C; $[\alpha]^{22}_D$ −39.1° (*c* 0.33, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.13, 0.16, 0.17, 0.19 (4 × s, 6H), 0.90 (s, 3.6H, α anomer), 0.93 (s, 5.4H, β anomer), 2.11 (s, 1.2H), 2.19 (s, 1.8H), 3.32 (d, 0.6H, $J_{2,3}$ = 4.3 Hz), 3.33 (d, 0.4H, $J_{2,3}$ = 4.3 Hz), 3.52 (dd, 0.6H, $J_{3,4}$ = 2.2 Hz), 3.61 (dd, 0.4H, $J_{3,4}$ = 1.9 Hz), 3.82 (s, 1.8H), 3.85 (s, 1.2H), 4.41 (d, 0.6H), 4.61 (d, 0.4H), 5.43 (d, 0.6H, $J_{1,2}$ = 0.9 Hz), 5.53 (d, 0.4H, $J_{1,2}$ < 0.7 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −5.2, −5.1, −4.3, −4.2, 18.1, 23.4, 23.7, 25.6, 25.7, 40.6, 40.9, 43.2, 44.3, 52.3, 52.6, 74.3, 74.6, 96.8, 97.4, 168.7, 180.7; IR (film) 1760, 1700, 1680 cm^{-1}; mass spectrum (CI) *m*/*z* 316 $(MH)^+$. Anal. Calcd for $C_{14}H_{25}NO_5Si$: C, 53.30; H, 7.99; N, 4.44. Found: C, 53.18; H, 7.78; N, 4.28.

Continued elution of the chromatography column provided compound **22** (450 mg, 15%) also as a solid: mp 133−135 °C; $[\alpha]^{22}_D$ +83.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 1.86 (s, 3H), 2.45 (s, 3H), 3.70 (s, 3H), 4.86 (d, 1H, $J_{4,3}$ = 8.5 Hz), 4.88 (dd, 1H, $J_{2,3}$ = 8.0 Hz), 5.00 (ddd, 1H), 5.42 (d, 1H, $J_{1,2}$ = 3.5 Hz), 6.47 (d, 1H, $J_{NH,3}$ = 7.9 Hz), 7.33 (d, 2H), 7.80 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, 17.9, 21.6, 22.4, 25.4, 52.0, 52.2, 75.3, 80.0, 94.2, 128.0, 129.8, 133.2, 145.1, 170.1, 170.6; IR (film) 3360, 3280, 1750, 1665, 1540 cm^{-1}; mass spectrum (CI) *m*/*z* 488 $(MH)^+$. Anal. Calcd for $C_{21}H_{33}NO_8SSi$: C, 51.72; H, 6.82; N, 2.87; S, 6.58. Found: C, 51.55; H, 6.66; N, 2.91; S, 6.68.

Methyl *N*-Acetyl-2,3-aziridino-2,3-dideoxy β-D-lyxofuranuronate (23). A solution of compound **21** (560 mg, 1.77 mmol) in CH_2Cl_2 (15 mL) was treated at −65 °C and under a nitrogen atmosphere with tetrabutylammonium fluoride (600 mg, 1.9 mmol). The reaction mixture was gradually allowed to come to rt over 1.5 h. The solvent was then removed under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate), affording compound **23** (275 mg, 77%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.11 (s, 3H), 3.43 (d, 1H, $J_{2,3}$ = 4.3 Hz), 3.65 (dd, 1H, $J_{3,4}$ = 1.9 Hz), 3.86 (s, 3H), 3.96 (m, 1H, exchangeable with D_2O), 4.74 (d, 1H), 5.60 (d, 1H, $J_{1,2}$ = 0.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 40.7, 43.5, 52.7, 74.5, 96.1, 169.1, 180.6; IR (film) 3400, 1756, 1700 cm^{-1}; mass spectrum (HRCI) calcd for $C_8H_{12}NO_5$ $(MH)^+$ *m*/*z* 202.0715, found 202.0711.

(1*S*,4*S*,5*R*)-*N*-Acetyl-4-(methoxycarbonyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (24). To a mixture of 4-methylmorpholine *N*-oxide (130 mg, 1.11 mmol) and powdered 4 Å molecular sieves (372 mg) were successively added under nitrogen at rt a solution of compound **23** (180 mg, 0.90 mmol) in acetonitrile (7 mL) and TPAP (26 mg, 0.09 mmol). The reaction mixture was stirred for 4 h, after which it was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and filtered through a pad of silica gel affording, after removal of the solvent *in vacuo*, compound **24** (120 mg, 67%) as a colorless oil which slowly crystallized on standing. An analytical sample of **24** was obtained by preparative TLC on silica gel using heptane−ethyl acetate (1:4) as eluent: mp 94−95 °C; $[\alpha]^{27}_D$ −56.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.70 (d, 1H, $J_{1,5}$ = 4.1 Hz), 3.89 (s, 3H), 4.03 (dd, 1H, $J_{5,4}$ = 3.4 Hz), 4.74 (d, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 23.4, 37.3, 40.8, 53.1, 75.2, 166.2, 167.6, 178.9; IR (film) 1800, 1768, 1715 cm^{-1}; mass spectrum (CI) *m*/*z* 200 $(MH)^+$. Anal. Calcd for $C_8H_9NO_5$.0.05 C_7H_{16}: C, 49.12; H, 4.84; N, 6.86. Found: C, 49.32; H, 5.05; N, 6.51.

Methyl [*tert*-Butyldimethylsilyl 2,3-aziridino-*N*-(benzyloxycarbonyl)-2,3-dideoxy-α,β-D-lyxofuranosid]uronate (25). To a solution of crude aziridine β-**19** (2.37 g of the crude product containing ∼30% of **20** and ∼55−60% of β-**19**),[31] triethylamine (2.43 mL, 17.3 mmol), and DMAP (106 mg, 0.87 mmol) in DMF (40 mL) was added dropwise at 0 °C a solution of benzyl chloroformate (2.47 mL, 17.3 mmol) in DMF (3 mL). The reaction mixture was stirred for 30 min at 0 °C and then for 2.5 h at 20 °C, at which point the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate and water, the phases were separated, and the organic phase was dried over Na_2SO_4. Removal of the solvent *in vacuo* and chromatography of the residue on silica gel (heptane−ethyl acetate 2:1) gave compound **25** as a white solid (2.03 g, ∼95% yield based on the estimated weight of **19** in the crude starting material) containing a small amount of the α anomer (<10% by ^{1}H NMR) which was used as such in the following step. For analytical purposes, the major β anomer was isolated in pure form by preparative chromatography of an aliquot of **25** (heptane−ethyl acetate 2:1): mp 86−87 °C; $[\alpha]^{22}_D$ − 27.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.18 (s, 3H), 0.92 (s, 9H), 3.32 (dd, 1H, $J_{1,2}$ = 1.4 Hz, $J_{2,3}$ = 4.6 Hz), 3.55 (dd, 1H, $J_{3,4}$ = 2.3 Hz), 3.77 (s, 3H), 4.40 (d, 1H), 5.11 (s, 2H), 5.44 (d, 1H), 7.33 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.2, 18.1, 25.7, 41.9, 43.9, 52.3, 68.2, 74.5, 97.3, 128.2, 128.4, 135.5, 161.0, 168.2; IR (film) 1765, 1730 cm^{-1}; mass spectrum (CI) *m*/*z* 408 $(MH)^+$. Anal. Calcd for $C_{20}H_{29}NO_6Si$. 0.15 H_2O: C, 58.55; H, 7.20; N, 3.41. Found: C, 58.28; H, 7.14; N, 3.29.

Methyl 2,3-Aziridino-*N*-(benzyloxycarbonyl)-2,3-dideoxy-β-D-lyxofuranuronate (26). Following the same procedure as for the preparation of **23** from **21**, compound **25** (937 mg, 2.3 mmol) afforded **26** (510 mg, 75%) as a white solid after chromatography of the crude reaction mixture on silica gel (heptane−ethyl acetate 1:1). Only traces of the α anomer could be observed by ^{1}H NMR: mp 105−107 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.27 (d, 1H, $J_{2,3}$ = 3.8 Hz), 3.57 (dd, 1H, $J_{3,4}$ = 1.9 Hz), 3.62 (s, 3H), 4.21 (m, 1H, exchangeable with D_2O), 4.73 (d, 1H), 4.96 (d, 1H, J_{gem} = 12.1 Hz), 5.19 (d, 1H), 5.64 (s, 1H), 7.35 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 42.7, 52.4, 68.5, 73.8, 95.5, 128.5, 128.6, 135.3, 159.6, 169.8; IR (film) 3450, 1760, 1730 cm^{-1}; mass spectrum (EI) *m*/*z* 293 (M^+). Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.28; H, 5.29; N, 4.59.

(1*S*,4*S*,5*R*)-*N*-(Benzyloxycarbonyl)-4-(methoxycarbonyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (27). Using the same procedure as for the preparation of **24**, compound **26** (230 mg, 1.96 mmol) was oxidized using TPAP and 4-methylmorpholine *N*-oxide, affording lactone **27** (290 mg, 77%) as a colorless oil which crystallized on standing: mp 90−92 °C; $[\alpha]^{27}_D$ −25.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.59 (d, 1H, $J_{1,5}$ = 4.0 Hz), 3.78 (s, 3H), 4.01 (dd, 1H, $J_{5,4}$ = 3.6 Hz), 5.00 (d, 1H), 5.10 (d, 1H, J_{gem} = 12.1 Hz), 5.17 (d, 1H), 7.36 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9, 41.3, 52.9, 69.4, 74.9, 128.4, 128.6, 128.7, 134.6, 158.5, 165.7, 167.4; IR (film) 1805, 1765, 1735 cm^{-1}; mass spectrum (EI) *m*/*z* 291 (M^+). Anal. Calcd for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.81. Found: C, 57.53; H, 4.36; N, 4.66.

Dimethyl (2*S*,3*R*,4*S*)-4-Hydroxy-2,3-iminopentane-1,5-dioate (28). To a solution of compound **24** (160 mg, 0.8 mmol) in anhydrous methanol (10 mL) was added at −20 °C and under nitrogen boron trifluoride etherate (200 μL, 1.6 mmol). The reaction mixture was allowed to come to rt over 3 h, after which it was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (15 mL), and the solution was neutralized by addition of aqueous $NaHCO_3$ (8 mL of a 0.2 M solution). After separation of the phases, the aqueous phase was extracted with ethyl acetate (2 × 10 mL), and the combined organic phases were dried over Na_2SO_4. Evaporation of the solvents *in vacuo* and column chromatography of the residue on silica gel (ethyl acetate) afforded compound **28** (95 mg, 62%) as a colorless oil: $[\alpha]^{27}_D$ +97.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.52 (dd, 1H), 2.63 (m, 2H, exchangeable with D_2O), 2.86 (d, 1H, $J_{2,3}$ = 6.0 Hz), 3.79 (s, 3H), 3.80 (s, 3H), 4.24 (d, 1H, $J_{4,3}$ = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.2, 40.1, 52.8, 52.9, 69.7, 171.0, 172.6; IR (film) 3370, 3280, 1740 cm^{-1}; mass spectrum (CI) *m*/*z* 190 $(MH)^+$. Anal. Calcd for $C_7H_{11}NO_5$·0.07C_7H_{16}: C, 45.86; H, 6.23; N, 7.14. Found: C, 45.82; H, 5.97; N, 6.84.

Methyl (2*S*,3*S*,4*R*)-Tetrahydro-3-acetamido-4-(ethylthio)-5-oxo-2-furancarboxylate (29). To a solution of compound **24** (30 mg, 0.15 mmol) in ethanethiol (1 mL) and chloroform (1 mL) was added at −25 °C under nitrogen boron trifluoride etherate (18 μL, 0.15 mmol). The reaction mixture was slowly brought to rt over 4 h. It was then diluted with ethyl acetate (5 mL), and aqueous $NaHCO_3$ (1.5 mL of a 0.2 M solution) was added. The phases were separated, the aqueous phase was extracted with ethyl acetate (2 × 5 mL),

and the combined organic extracts were dried over Na_2SO_4. Removal of the solvents under reduced pressure and chromatography of the residue on silica gel (heptane−ethyl acetate 4:6) provided **29** (28 mg, 71%) as a white solid: mp 88−90 °C; $[\alpha]^{22}_D$ +95.3° (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.4 Hz), 2.02 (s, 3H), 2.78 (m, 2H), 3.71 (d, 1H, $J_{3,4}$ = 5.8 Hz), 3.81 (s, 3H), 4.84 (ddd, 1H, $J_{3,NH}$ = 8.1 Hz, $J_{3,2}$ = 6.2 Hz), 5.25 (d, 1H, $J_{2,3}$ = 6.5 Hz), 7.00 (d, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.2, 22.8, 25.4, 45.0, 53.0, 53.7, 77.4, 167.9, 170.7, 172.3; IR (film) 3280, 1790, 1748, 1665, 1545 cm^{-1}; mass spectrum (CI) *m*/*z* 262 $(MH)^+$. Anal. Calcd for $C_7H_{11}NO_5 \cdot 0.02C_7H_{16}$: C, 46.32; H, 5.88; N, 5.31; S, 12.15. Found: C, 46.57; H, 5.86; N, 5.15; S, 12.48.

Dimethyl (2*S*,3*S*,4*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-4-hydroxy-3-methoxypentane-1,5-dioate (31) and Methyl (2*S*,3*S*,4*S*)-Tetrahydro-4-[*N*-(benzyloxycarbonyl)amino]-3-methoxy-5-oxo-2-furancarboxylate (32). To a solution of **27** (96 mg, 0.33 mmol) in anhydrous methanol (7 mL) was added at 0 °C under nitrogen boron trifluoride etherate (80 μL, 0.65 mmol). The reaction mixture was allowed to come to rt, stirring was maintained for 30 min, and the reaction mixture was then heated to 50 °C for 90 min. After being cooled to 0 °C, the solution was diluted with ethyl acetate (15 mL), saturated aqueous $NaHCO_3$ was added (5 mL), and the phases were separated. The aqueous phase was further extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were dried over Na_2SO_4. Removal of the solvent under reduced pressure left an oily residue which was purified by chromatography on silica gel using heptane−ethyl acetate (1:1) as eluent. Lactone **32** (16 mg, 15%), a colorless oil, was the first product to be eluted: $[\alpha]^{22}_D$ +9.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.50 (s, 3H), 3.86 (s, 3H), 4.23 (dd, 1H), 4.32 (dd, 1H, $J_{3,4}$ = 5.5 Hz, $J_{4,NH}$ = 7.7 Hz), 4.77 (d, 1H, $J_{2,3}$ = 4.5 Hz), 5.14 (s, 2H), 5.50 (d, 1H, exchangeable with D_2O), 7.35 (s, 5H); IR (film) 3356, 1800, 1740, 1718, 1525 cm^{-1}; mass spectrum (HREI) calcd for $C_{15}H_{17}NO_7$ *m*/*z* 323.1004, found 323.1008.

Continued elution of the column afforded compound **31** (70 mg, 60%), slightly contaminated by its lactonic form **32**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.31 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 4.00 (dd, 1H, $J_{2,3}$ = 1.4 Hz, $J_{3,4}$ = 8.3 Hz), 4.10 (d, 1H), 4.86 (dd, 1H, $J_{2,NH}$ = 8.9 Hz), 5.13 (s, 2H), 5.66 (d, 1H, exchangeable with D_2O), 7.35 (s, 5H); IR (film) 3390, 1740, 1520 cm^{-1}; mass spectrum (CI) *m*/*z* 356 $(MH)^+$.

Diethyl (2*S*,3*S*,4*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-ethoxy-4-hydroxypentane-1,5-dioate (33) and Ethyl (2*S*,3*S*,4*S*)-Tetrahydro-4-[*N*-(benzyloxycarbonyl)amino]-3-ethoxy-5-oxo-2-furancarboxylate (34). A solution of **27** (131 mg, 0.45 mmol) in anhydrous ethanol (12 mL) was treated with boron trifluoride etherate (140 μL, 1.14 mmol) and heated for 45 h at 70 °C. At the end of the reaction period, the reaction mixture was cooled to 0 °C and worked up as described for compounds **31** and **32**. Chromatography of the crude product on silica gel (heptane−ethyl acetate 3:2) afforded compound **34** (25 mg, 16%), an amorphous white solid as a minor product: $[\alpha]^{22}_D$ +6.8° (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, J = 6.8 Hz), 1.32 (t, 3H, J = 7.1 Hz), 3.68 (m, 2H), 4.30 (m, 4H), 4.74 (d, 1H, $J_{2,3}$ = 4.2 Hz), 5.13 (s, 2H), 5.50 (d, 1H, exchangeable with D_2O, $J_{4,NH}$ = 6.2 Hz), 7.35 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 15.4, 57.1, 62.7, 66.6, 67.9, 79.2, 81.8, 128.4, 128.6, 128.8, 157.6, 167.8, 171.4; IR (film) 3360, 1806, 1730, 1525 cm^{-1}; mass spectrum (CI) *m*/*z* 352 $(MH)^+$. Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.31; H, 6.31; N, 3.97.

Continued elution of the chromatography column yielded the major product, compound **33** (105 mg, 58%), as an oil, slightly contaminated by **34**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.07 (t, 3H, J = 7.0 Hz), 1.30 (2 × t, 6H, J = 7.1 Hz), 3.45 (m, 2H), 3.91 (m, 1H, exchangeable with D_2O), 4.07 (m, 2H), 4.24 (m, 2H), 4.71 (d, 1H, $J_{2,NH}$ = 9.0 Hz), 5.12 (2H, J_{gem} = 12.2 Hz), 5.70 (d, 1H, exchangeable with D_2O), 7.36 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 15.4, 54.5, 61.7, 61.9, 67.5, 67.9, 70.6, 81.1, 128.2, 128.3, 128.6, 136.0, 157.1, 170.7, 172.3; IR (film) 3390, 1740, 1520 cm^{-1}; mass spectrum (HRCI) calcd for $C_{19}H_{28}NO_8$ *m*/*z* 398.1815, found 398.1784.

1-Benzyl 5-Methyl (2*S*,3*S*,4*S*)-3-(Benzyloxy)-2-[*N*-(benzyloxycarbonyl)amino]-4-hydroxypentanedioate (35). To a solution of **27** (116 mg, 0.4 mmol) in $CHCl_3$ (1.5 mL) and benzyl alcohol (1.5 mL) was added at 0 °C under nitrogen boron trifluoride etherate (60 μL, 0.48 mmol). The reaction mixture was stirred for 30 min at rt and then heated at 60 °C for 2 h. After being cooled to 0 °C, the solution was worked up in the manner described for **31** and **32**. The resulting crude product was purified by chromatography on silica gel (heptane−ethyl acetate 9:1 followed by 3:1) affording **35** (80 mg, 39%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.86 (m, 1H, exchangeable with D_2O), 4.14 (m, 1H), 4.17 (d, 1H, J_{gem} = 11.0 Hz), 4.23 (dd, 1H, $J_{2,3}$ = 1.3 Hz, $J_{3,4}$ = 8.4 Hz), 4.30 (d, 1H), 4.82 (dd, 1H, $J_{2,NH}$ = 9.1 Hz), 5.12 (s, 2H), 5.14 (s, 2H), 5.71 (d, 1H, exchangeable with D_2O), 7.25−7.37 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.1, 55.2, 68.2, 68.4, 71.0, 74.6, 81.3, 128.5, 128.7, 128.8, 128.9, 129.0, 129.1, 129.2, 129.3, 129.4, 135.4, 136.4, 137.5, 157.7, 171.0, 173.1; IR (film) 3425, 3350, 1730, 1520 cm^{-1}; mass spectrum (CI) *m*/*z* 490 $(MH - H_2O)^+$.

1-Benzyl 5-Methyl (2*S*,3*S*,4*S*)-4-Acetoxy-3-(benzyloxy)-2-[*N*-(benzyloxycarbonyl)amino]pentanedioate (36). A solution of **35** (56 mg, 0.11 mmol) in pyridine (2 mL) and acetic anhydride (0.3 mL) was kept at 5 °C for 3 days. The solvents were then removed under reduced pressure, and the residue was purified by chromatography on silica gel (heptane−ethyl acetate 3:1), yielding **36** (55 mg, 91%) as a colorless oil: $[\alpha]^{22}_D$ −5.6° (*c* 0.25, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.11 (s, 3H), 3.67 (s, 3H), 4.18 (d, 1H, J_{gem} = 10.9 Hz), 4.30 (d, 1H), 4.45 (dd, 1H, $J_{2,3}$ = 1.4 Hz, $J_{3,4}$ = 8.4 Hz), 4.74 (dd, 1H, $J_{2,NH}$ = 10.0 Hz), 4.98 (d, 1H), 5.10 (s, 2H), 5.13 (s, 2H), 5.53 (d, 1H, exchangeable with D_2O), 7.05−7.37 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 52.1, 54.4, 66.8, 67.2, 70.3, 73.8, 77.7, 127.3, 127.4, 127.7, 127.9, 128.0, 128.2, 134.4, 136.0, 155.9, 168.9, 169.1, 169.6; IR (film) 3356, 1750, 1725, 1520 cm^{-1}; mass spectrum (CI) *m*/*z* 550 $(MH)^+$. Anal. Calcd for $C_{30}H_{31}NO_9$: C, 65.57; H, 5.69; N, 2.55. Found: C, 65.35, H, 5.93; N, 2.44.

1-Benzyl 5-Methyl (2*S*,3*R*,4*S*)-2,3-[*N*-(Benzyloxycarbonyl)imino]-4-hydroxypentanedioate (37). To a solution of **27** (54 mg, 0.18 mmol) in $CHCl_3$ (1 mL) and benzyl alcohol (1.5 mL) was added at 0 °C under nitrogen boron trifluoride etherate (23 μL, 0.18 mmol). The reaction mixture was then stirred for 3 h at rt and worked up in the manner described for **31** and **32**. The crude product was purified by chromatography on silica gel (heptane−ethyl acetate 9:1 followed by 4:1 and then 2:1) affording **37** (52 mg, 70%) as a colorless oil: $[\alpha]^{22}_D$ −14.6° (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.97 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 6.6 Hz), 3.16 (m, 1H, exchangeable with D_2O), 3.33 (d, 1H), 3.57 (s, 3H), 4.43 (d, 1H), 5.15 (s, 2H), 5.21 (2 × d, 2H, J_{gem} = 12.1 Hz), 7.35−7.37 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.3, 44.7, 53.1, 67.9, 68.4, 69.3, 128.6, 128.9, 129.0, 135.3, 135.4, 161.2, 166.9, 171.8; IR (film) 3480, 1740 cm^{-1}; mass spectrum (CI) *m*/*z* 400 $(MH)^+$. Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 62.87; H, 5.44; N, 3.64.

Acknowledgment. We thank the French Ministry of Defence for generous financial support (Contract No. 93/133) and for a fellowship (P.D.) as well as Prof. P. Potier for discussions and encouragement.

JO951983Z