2,3-Aziridino-2,3-dideoxy-D-ribono-γ-lactone 5-Phosphonate: Stereocontrolled Synthesis from D-Lyxose and Unusual Aziridine Ring Opening

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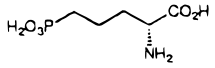
Received December 16, 1996⊗

The synthesis of (1*R*,4*S*,5*S*)-*N*-(benzyloxycarbonyl)-4-[(diethoxyphosphinyl)methyl]-3-oxa-6-azabicyclo-[3.1.0]hexan-2-one (**23**), a new member of the 2,3-aziridino γ-lactone family of compounds, was achieved in 15 steps from D-lyxose. Like all aziridino γ-lactones known so far, **23** reacted with a soft nucleophile (ethanethiol) to give exclusively the product of aziridine ring opening at C-2 (**24**). On the other hand, hard nucleophiles (alcohols) did not react directly with the aziridine ring of **23** but appeared to promote intramolecular attack of the aziridine ring at C-3 by the C-5 phosphonate group, resulting, after hydrolytic workup, in formation of the 2-amino-3-hydroxy-D-ribono-1,4-lactone derivatives **25** and **26**, instead of the expected 2-amino-3-alkoxy-D-xylono-1,4-lactone derivatives.

Introduction

Dysfunction or hyperactivity of the *N*-methyl-D-aspartate (NMDA) receptor, one of three subclasses of ionotropic glutamate receptors of the central nervous system,[1] has been implicated in a large number of neurological disorders (e.g., epilepsy, Huntington's chorea, Alzheimer's and Parkinson's disease, AIDS-related dementia, and ischemic events resulting from stroke or cerebral trauma).[2,3] The development of compounds that can antagonize the action of glutamate at this receptor thus represents an important objective for the treatment of such disorders. Presently, one of the major classes of NMDA receptor antagonists consists of molecules belonging to the (*R*)-2-amino-5-phosphonopentanoic acid (D-AP5, **1**) family.[4] While these compounds may be considered isosteres of L-glutamic acid, they are distinguished from the latter in having the non-natural (i.e., D) configuration, the L isomer of AP5 being less active.



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The possibility of synthesizing variously substituted analogues of D-AP5 is essential for the discovery of more active and/or more selective ligands. For example, while the highly polar character of D-AP5 severely limits its penetration into the brain,[5] the introduction of unsaturation[6,7] on the D-AP5 backbone as well as formation of cyclic analogues[8−12] have been shown to have a highly favorable influence on brain penetration and consequently on *in vivo* activity. To date, however, very few studies concerning the synthesis of mono- and, especially, disubstituted derivatives of D-AP5 have been reported.[10,13−15]

We have recently described the synthesis of 3,4-disubstituted L-glutamic acid derivatives of type **3** by Lewis acid-catalyzed nucleophilic ring opening of the 2,3-aziridino γ-lactone 4-carboxylate **2**, the latter having, in turn, been synthesized from D-ribose (Scheme 1).[16] Compound **2** and other 2,3-aziridino γ-lactones[17,18] demonstrate remarkable regioselectivity with respect to nucleophilic attack of the aziridine ring, with soft nucleophiles reacting exclusively at the C-2 position while hard nucleophiles give the products of ring opening at C-3. In order to apply this methodology to the preparation of 3,4-disubstituted D-AP5 derivatives (i.e., of type **4**, Scheme 1), two major modifications needed to be brought to the starting 2,3-aziridino γ-lactone. The first was generation of such a derivative having the *ribo* configuration (as in **5**) rather than the *lyxo* configuration (as in **2**). The *ribo*

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⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1997.

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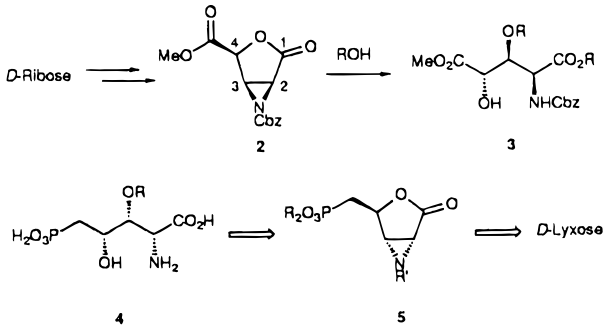
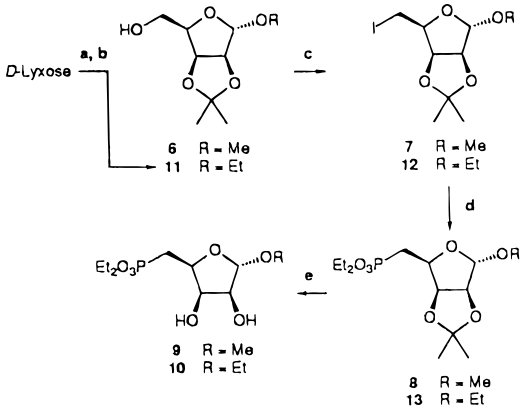
S0022-3263(96)02349-3 CCC: $14.00

Scheme 1. Synthesis of 3,4-Disubstituted L-Glutamic Acid Derivatives *via* Aziridine-γ-lactone Chemistry and Retrosynthetic Scheme for the Preparation of 3,4-Disubstituted Derivatives of D-AP5(1)



Scheme 2. Preparation of the 5-Phospho 2,3-Diol Precursor 10[a]



[a] Key: (a) EtOH, HCl; (b) acetone, HCl (54%); (c) I_2, PPh_3, imidazole, toluene, 80 °C, 1.5 h (R = Me, 75%, R = Et, 78%); (d) $P(OEt)_3$, 160 °C, 24 h (R = Me, 82%; R = Et, 85%); (e) I_2, EtOH, reflux, 10 h (R = Et, 66% based on consumed SM).

configuration would then assure generation of a D(rather than an L)-α-amino acid after nucleophilic opening of the aziridine ring at C-3 (via an S_N2 process) and of the lactone. Such a *ribo* configuration should normally be obtained if the methodology developed for the synthesis of **2** is applied to D-lyxose. Incorporation of a 5-phosphonate moiety in the *ribo* aziridino γ-lactone structure, as in **5**, was the second modification to be envisaged. In this paper, then, we describe the successful synthesis of the diethyl phosphonate *N*-Cbz derivative of **5** (i.e., **23**) and present results concerning the unusual reactivity pattern of this compound toward certain nucleophiles.

Results and Discussion

Preparation of the 2,3-aziridino-γ-ribonolactone 5-phosphonate 23. On the basis of our previous experience in synthesizing aziridino-γ-lactone **2**, it was judged more expedient to incorporate the C-5 phosphonate group on the sugar moiety before constructing the aziridine ring or introducing any of the substituents (azide, tosyl) necessary for this purpose for two reasons. First, the introduction of a phosphonate group would most likely require the use of phosphite reagents, incompatible with an azide functionality due to the possibility of Staudinger-type processes. Secondly, a reactive aziridine ring would probably not withstand the harsh phosphonylation conditions encountered, for example, in an Arbuzov reaction. The efficient synthesis of methyl 5-deoxy-5-*C*-(diethoxyphosphinyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside via a Michaelis−Arbuzov reaction of triethyl phosphite with its 5-iodoribofuranoside precursor has been reported.[19,20] We thus chose to apply this chemistry to the *lyxo* series in order to prepare the required phosphonate precursor **8** (Scheme 2) using as starting material methyl 2,3-*O*-isopropylidene-α-D-lyxofuranoside (**6**).[21] The 5-iodo derivative **7** has previously been prepared in two steps from **6** by tosylation of the free hydroxy group followed by reaction with sodium iodide at 115 °C for 66 h in a Parr bomb.[21] However, compound **7** can be prepared more conveniently and in as high yield (75%) by treating **6** with iodine, triphenylphosphine, and imidazole in toluene at 80 °C for 1.5 h.[22] Compound **7** obtained in this manner had an identical ^{1}H NMR spectrum and optical rotation as that prepared by the sodium iodide method. Compound **7** was then subjected to a Michaelis−Arbuzov reaction with triethyl phosphite using the modified procedure of Yamamoto and co-workers,[20] affording phosphonate **8** in excellent yield (85%).

With the phosphonate group in place, attention was next turned to incorporation of the 2,3-aziridine functionality. Attempted hydrolysis of the 2,3-*O*-isopropylidene moiety of **8** using a variety of acidic conditions (differing proportions of trifluoroacetic acid−water or hydrochloric acid−water, with or without heating) gave only mediocre yields of the desired diol **9**. Szarek and co-workers[23] have described the use of iodine in refluxing methanol as an efficient way of cleaving carbohydrate acetals. Application of this technique to **8**, however, led to complete recovery of starting material even after prolonged reflux. When methanol was replaced by higher-boiling ethanol in this reaction, complete cleavage of the isopropylidene group was finally obtained, as indicated by the ^{1}H NMR spectrum of the reaction mixture. However, this spectrum also showed that two compounds, the expected diol **9** and the product of transacetalization of the latter, **10**, had been formed in almost equal proportion. Though longer reaction times resulted in increased proportions of the ethyl anomer **10**, overall yields of diol suffered. Because **9** and **10** could not be separated by chromatography, the sequence of reactions was repeated using the ethyl furanoside **11** (prepared in one pot by reacting D-lyxose with ethanol and HCl at 60 °C for 30 min and then with acetone at 20 °C for 24 h)[24] as starting material. Thus, **11** was iodinated at C-5 to give **12**, which in turn underwent a Michaelis−Arbuzov reaction, affording **13**. Finally treatment of **13** with iodine for 10 h in refluxing ethanol provided diol **10** in moderate (40%) yield together with unreacted **13** (40%), which could be recycled after chromatographic separation of the two compounds.

We have previously found 2,3-cyclic sulfite derivatives of ribofuranosides to be excellent substrates for the

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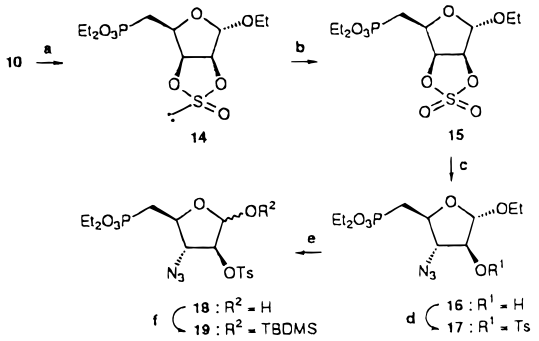
Scheme 3. Introduction of the C-3 Azide Function and Sequence of Protection/Deprotection Reactions[a]

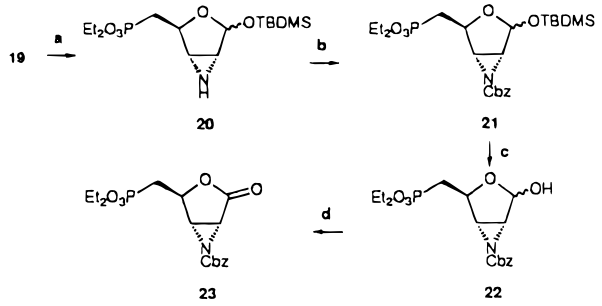


[a] Key: (a) $SOCl_2$, Et_3N, THF, −25 °C, 30 min; (b) $RuCl_3$, $NaIO_4$, rt, 2.5 h (84% from **10**); (c) NaN_3, DMF, 60 °C, 2.5 h then H_2SO_4, H_2O, THF, rt, 2 h (95%); (d) TsCl, pyr (95%); (e) CF_3CO_2H/H_2O 9/1, 50 °C, 5 d; (f) TBDMSCl, imidazole, DMF, rt, 24 h (82% based on **17**).

selective introduction of an azide function at C-3 of ribofuranosides, a necessary prelude to formation of the 2,3-aziridine ring.[16,25] The cyclic sulfite **14** of the lyxofuranoside 2,3-diol **10** was thus prepared by reaction of the latter with thionyl chloride and triethylamine in THF at −25 °C for 30 min (Scheme 3).[26] However, treatment of **14** with sodium azide in DMF or HMPA led to decomposition of starting material at temperatures greater than 100 °C and no reaction below 100 °C. The chemical instability of **14** is most probably the result of the acidity of the C-5 protons, due to the adjacent phosphonate group. In the presence of a basic reagent such as sodium azide, this results in parasitic reaction pathways. In order to increase the leaving group character of the cyclic sulfite moiety and, thus, hopefully decrease the temperature necessary for displacement by azide anion, compound **14** was oxidized to the cyclic sulfate **15** using catalytic ruthenium trichloride and sodium metaperiodate.[27−29] Compound **15**, obtained in 84% yield (based on diol **10**), then reacted smoothly with sodium azide in DMF at 60 °C to give, after acid hydrolysis of the intermediate 2-sulfate, the desired *trans* 3-azido-2-hydroxy derivative **16**.

At this point, the successful transformation of **16** into an aziridine-γ-lactone required a sequence of protection-deprotection reactions. Thus, the free 2-hydroxy group of **16** was first tosylated to give the azido tosylate **17** (Scheme 3), the immediate precursor of the aziridine ring. Next, replacement of the anomeric protecting group (ethyl) by an alkylsilyl group was necessary since the latter, unlike the former, can be removed under conditions mild enough not to affect an aziridine ring (e.g., by fluoride ion) prior to oxidation to the lactone.[16,25] To this end, the anomeric acetal function of **17** was carefully hydrolyzed using 9:1 trifluoroacetic acid−water at 50 °C for 108 h. The furanose product **18** was then O-silylated by treatment with *tert*-butyldimethylsilyl chloride and imidazole in DMF, providing **19** as a 3:2 mixture of α- and β-anomers, respectively, as estimated by ^{1}H NMR spectroscopy.

Scheme 4. Preparation of the 2,3-Aziridino γ-Lactone 5-Phosphonate 23[a]



[a] Key: (a) H_2, Pd/C, MeOH, rt, 2.5 h then Et_2NH, DMF, 105 °C, 6 h (74%); (b) CbzCl, Et_3N, DMF (81%); (c) nBu$_4$NF, CH_2Cl_2, −60 °C → 20 °C, 90 min (87%); (d) TPAP, NMO, 4 Å molecular sieves, CH_3CN, 20 °C, 3 h (86%).

Completion of the synthesis of the target molecule is shown in Scheme 4. Compound **19** was efficiently transformed into the 2,3-aziridine **20** by first reducing, via catalytic hydrogenation, the azide function to an amine. The latter, not isolated, was immediately cyclized to **20** by the action of diethylamine in DMF at 105 °C. We have previously shown that the benzyloxycarbonyl moiety is an excellent blocking/activating group for the NH function of aziridino γ-lactones[16,18] and can, moreover, be easily removed under mild, nonhydrolytic conditions in the final step of amino acid synthesis. For these reasons, the *N*-Cbz derivative of **20** was prepared by treating the latter with benzyl chloroformate and triethylamine in DMF. The product, **21**, was then desilylated using tetrabutylammonium fluoride in dichloromethane, providing aziridinofuranose **22**. Oxidation of the latter with tetrapropylammonium perruthenate[30] (TPAP)/4-methylmorpholine *N*-oxide (NMO) produced the desired γ-butyrolactone **23** in 86% yield. Spectroscopic and analytical data for **23** were in complete accord with the proposed structure. In particular, characteristic signals for the lactone functionality were observed in the IR (1800 cm^{-1}) and ^{13}C NMR (168.2 ppm) spectra of **23**, while the ^{1}H NMR spectrum showed the absence of coupling between H-3 and H-4, indicative of a *trans* arrangement for these protons.

Reactivity of 23 toward Nucleophiles. Before attempting to prepare D-AP5 analogues of type **4** from **23**, we first investigated the behavior of the latter toward nucleophiles. One of the peculiarities of aziridino γ-lactones is their propensity to react with soft or hard nucleophiles regioselectively at C-2 or C-3, respectively. Thus, the aziridino γ-lactone 4-methyl carboxylate **2**,[16] as well as its 4-(methoxymethyl) analogue,[17,18] react with soft nucleophiles (e.g., thiols) in the presence of a Lewis acid (boron trifluoride etherate) exclusively at C-2 to give 2-substituted 3-aminobutyrolactones as products. In contrast, under the same conditions, these aziridino γ-lactones react with hard nucleophiles (e.g., alcohols) to give only the products of aziridine ring opening at C-3, that is, 3-substituted 2-aminobutyrolactones. The latter are formed via a lactone ring-opened intermediate (i.e., of type **3**) that, depending on the workup conditions of the reaction, can recyclize to the lactone form.[16,18]

We were thus very curious to see if the *ribo* aziridino γ-lactone 5-phosphonate **23** was subject to the same

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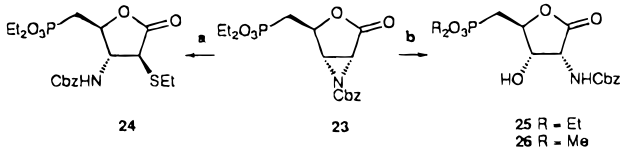
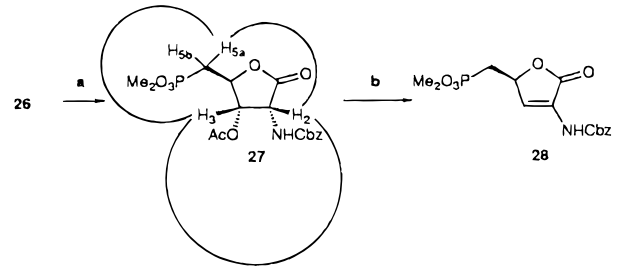
Scheme 5. Reactivity of the 2,3-Aziridino γ-Lactone 23 toward Representative Soft and Hard Nucleophiles[a]



[a] Key: (a) EtSH, 2 equiv of BF_3·OEt_2, 20 °C, 3 h (87%); (b) ROH, 2 equiv of BF_3·OEt_2, 60 °C, 5 h then evaporation and neutralization with $NaHCO_3$ (R = Et: 40%; R = Me: 33%).

Scheme 6. Structural Elucidation of 26. Correlations between H-2, H-3, and H-5$_a$ for Acetyl Derivative 27 Determined by 1D-NOESY Experiment[a]

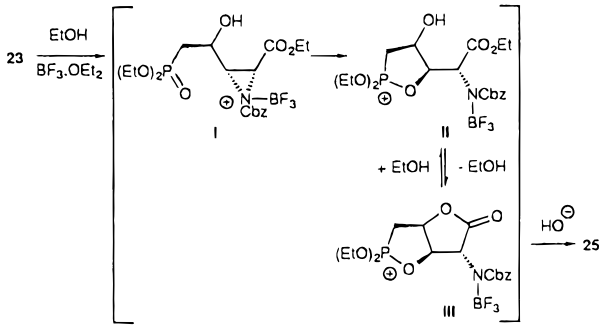


[a] Key: (a) Ac_2O, pyridine, 4 °C, 15 h (100%); (b) silica gel, AcOEt (78%).

regioselectivity of ring opening as the *lyxo* aziridino γ-lactone 4-carboxylate **2**. Although a full study of the reactivity of **23** toward nucleophiles has not yet been completed, we were very gratified to observe that reaction of **23** with a representative soft nucleophile, ethanethiol, gave, in the presence of 2 equiv of BF_3 etherate, exclusively the product of C-2 ring opening, **24** (Scheme 5). The presence of the alkylthio group at C-2 gives rise in the ^{1}H NMR spectrum to a characteristic high-field doublet (δ 3.87). The need for an additional equivalent of BF_3 etherate in this reaction is probably due to the presence of the phosphonate group with which this Lewis acid can also complex.

In contrast, a surprising result was obtained when **23** was treated with a hard nucleophile, ethanol, in the presence of 2 equiv of BF_3 etherate. A single compound (**25**) was obtained for which the ^{1}H NMR data did not show the expected incorporation of a supplementary ethoxy group but, instead, suggested the presence of a hydroxy group at C-3 of the lactone ring. That the latter was still intact after this reaction was clear from the IR (which showed a lactone band at 1790 cm^{-1}) and the ^{13}C NMR spectra (showing a lactone carbonyl resonance at 171.9 ppm) of **25**. Interestingly, the use of methanol instead of ethanol in this reaction also gave a 3-hydroxy derivative (**26**) that had for the most part undergone transesterification to the dimethyl phosphonate. In order to firmly establish both the regio- and stereochemistry of **25** and **26**, the latter was acetylated to give **27** (Scheme 6). In the ^{1}H NMR spectrum of crude **27**, H-2 appeared at 4.28 ppm as a pair of doublets due to coupling with H-3 and NH, a pattern typical of products resulting from aziridine ring opening at C-3. Surprisingly, NOESY experiments, which demonstrated correlations between H-3 and H-5, H-2 and H-5, and H-2 and H-3, proved that the C-2 and C-3 substituents of **27** (and, by analogy of **25** and **26**) were in a *cis* (i.e., *ribo*) configuration and *trans* to the C-4 substituent. When **27** was subjected to chromatography on silica gel, only the product of acetic acid elimination, furanone **28**, could be isolated, further corroborating the structural assignments of **25**, **26**, and **27**.

Scheme 7. Proposed Mechanism for Formation of 25 from 23



Compared to **2**, the reaction of *ribo* aziridino γ-lactone 5-phosphonate **23** with alcohols is thus unusual in two respects.[31] First, regardless of the alcohol used, only the product arising from opening of the aziridine ring by hydroxide is obtained. This probably occurs during the course of the basic, aqueous hydrolytic workup of the reaction mixture. Secondly, whereas the typical S_N2 opening of the aziridine ring of aziridino γ-lactones gives substituents having a *trans* relationship at C-2 and C-3, a *cis* relationship is observed in the case of products **25** and **26** arising from **23**. These observations may be rationalized by invoking anchimeric assistance by the phosphonate group of **23** in opening of the aziridine ring (Scheme 7).[32] Thus, as shown in our previous studies,[16,18] the first step in the reaction of aziridino γ-lactones with alcohols in the presence of a Lewis acid is opening of the lactone ring to give a 4-hydroxy-2,3-aziridino ester. In the case of compound **23**, this would correspond to a structure of type I. With the resulting release of ring strain, the oxygen atom of the phosphonate group of intermediate I is now favorably oriented to participate in opening of the aziridine ring to give intermediate II. The latter is apparently insensitive to further nucleophilic attack by the alcohol (except for eventual transesterification when an alcohol other than ethanol is used). Evaporation of the reaction mixture leads, as we have also previously observed in analogous systems,[18] to relactonization (intermediate III). Base workup would then provoke hydrolytic cleavage of III, resulting in introduction of a hydroxy group at C-3 *cis* to the NCbz moiety.

In conclusion, we have realized the synthesis, from D-lyxose, of a 2,3-aziridino γ-lactone 5-phosphonate (**23**), a potential precursor to novel 3,4-disubstituted analogues (**4**) of the non-natural but pharmacologically important phosphono D-amino acid, D-AP5 (**1**). Preliminary reactivity studies of **23** indicate that, like all members of the aziridino γ-lactone family known so far, nucleophilic attack by a soft nucleophile (e.g., a thiol) occurs exclusively at C-2. In contrast, whereas hard nucleophiles

(31) We have observed that the *lyxo* analogue of **23** reacts with alcohols in the expected fashion, i.e., by S_N2 nucleophilic opening of the aziridine ring at C-3, to give the *trans*-2-amino-3-alkoxybutyrolactone derivative, with no participation by the C-5 phosphonate group. Details of this work will be published elsewhere.

(32) Although unusual, this intramolecular aziridine ring opening is not entirely unprecedented since Ho and co-workers have described such a reaction with a benzyl ester group or a carboxamide. Ho, M.; Chung, J. K. K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513.

(e.g., alcohols) attack aziridino γ-lactones such as **2** at C-3, such reagents apparently lead, in the case of **23**, to formation of a relatively stable intermediate resulting from intramolecular attack of the aziridine ring by the phosphonate group, the overall product of the reaction being, after hydrolytic workup, *cis* 2-amino-3-hydroxybutyrolactones of type **25**. The latter represents a strategically important synthon (after lactone ring opening) for the preparation of 3,4-dihydroxy and dialkoxy D-AP5 derivatives of type **4**. This goal is currently being pursued.

Experimental Section

General Methods. 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). ^1H NMR and ^{13}C NMR chemical shifts are given as δ values with reference to Me_4Si, which was used as internal standard except in the case of silylated samples. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with UV light (254 nm) and 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. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

Methyl 5-Deoxy-5-iodo-2,3-*O*-isopropylidene-α-D-lyxofuranoside (7). A solution of compound **6**[21] (5.8 g, 28.4 mmol), iodine (10.1 g, 39.8 mmol), triphenylphosphine (11.2 g, 42.7 mmol), and imidazole (5.8 g, 85.2 mmol) in toluene (120 mL) was heated at 80 °C for 1.5 h. The reaction mixture was cooled to rt, the supernatant phase was removed by decantation, and the pasty white residue was partitioned between chloroform and water. Residual iodine was removed by addition of solid sodium thiosulfate pentahydrate (until disappearance of brown color), and the phases were separated. The organic phases (toluene, chloroform) were combined, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The oily residue was triturated with ether, and the resulting precipitate of triphenylphosphine oxide was removed by filtration through Celite. The filtrate was purified by chromatography on silica gel (heptane followed by heptane−ethyl acetate 9:1), affording the 5-iodo derivative **7** (6.7 g, 75%) as a colorless oil: $[\alpha]^{25}_D$ +71.2 (*c* 3.0, CH_3OH) (lit.[21] $[\alpha]^{24}_D$ +72.6 (*c* 2.88, CH_3OH)); ^1H NMR (250 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.46 (s, 3H), 3.28 (dd, J = 7.0, 9.7 Hz, 1H), 3.34 (s, 3H), 3.36 (dd, J = 7.5, 9.7 Hz, 1H), 4.20 (pseudo dt, J = 3.4, 7.1 Hz, 1H), 4.60 (d, J = 5.8 Hz, 1H), 4.75 (dd, J = 5.8, 3.4 Hz, 1H), 4.92 (s, 1H); mass spectrum (EI) *m*/*z* 314 [M^+].

Methyl 5-Deoxy-5-*C*-(diethoxyphosphinyl)-2,3-*O*-isopropylidene-α-D-lyxofuranoside (8). Compound **7** (6.64 g, 21.1 mmol) was dissolved in triethyl phosphite (12 mL, freshly distilled over sodium), and the solution was heated at 160 °C under a constant stream of nitrogen. After 15 h, fresh triethyl phosphite (6 mL) was added to the reaction mixture, and the latter was heated for a further 9 h. The solvent was then removed under reduced pressure, and the residue was purified by chromatography on silica gel (ethyl acetate−heptane 3:1 followed by 4:1 followed by ethyl acetate), providing compound **8** (5.6 g, 82%) as a colorless oil: $[\alpha]^{22}_D$ +41.7 (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.34 (t, J = 7.0 Hz, 6H), 1.45 (s, 3H), 2.21 (ddd, J(H,H) = 6.6, 15.2 Hz, J(H,P) = 18.0 Hz, 1H), 2.30 (ddd, J(H,H) = 6.8, 15.3 Hz, J(H,P) = 18.2 Hz, 1H), 3.33 (s, 3H), 4.13 (m, 4H), 4.51 (pseudo dq, J = 3.4, 6.7 Hz, 1H), 4.55 (d, J = 5.8 Hz, 1H), 4.67 (dd, J = 5.8, 3.4 Hz, 1H), 4.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 16.4, 25.0, 25.5 (d, J(C,P) = 140.0 Hz), 26.1, 54.5, 61.5, 61.9 (2 × d, J(C,P) = 6.0 Hz), 74.6, 84.3 (d, J(C,P) = 6.8 Hz), 85.1, 106.8, 112.5; IR (film) 1250, 1025, 970 cm^{-1}; mass spectrum (CI) *m*/*z* 325 [$M + 1^+$]. Anal. Calcd for $C_{13}H_{25}O_7P$: C, 48.15; H, 7.77; P, 9.55. Found: C, 47.94; H, 7.87; P, 9.44.

Ethyl 5-Deoxy-5-iodo-2,3-*O*-isopropylidene-α-D-lyxofuranoside (12). A suspension of D-lyxose (4.96 g, 33.0 mmol) in ethanol (180 mL) containing concentrated HCl (0.3 mL) was heated at 60 °C for 30 min. The resulting solution was cooled to 20 °C, stirred overnight, and then concentrated to half volume under vacuum. Acetone (80 mL) was added to the reaction mixture, and the latter was stirred for a further 24 h at 20 °C. The solution was neutralized with triethylamine, and the solvents were removed under vacuum. The oily residue was partitioned between ethyl acetate (150 mL) and water (150 mL), the phases were separated, and the organic phase was washed with water (100 mL) and dried over Na_2SO_4. Removal of the solvent under vacuum left crude ethyl 2,3-*O*-isopropylidene-α-D-lyxofuranoside (**11**, 3.9 g, 54%) as a colorless oil. Without further purification, the latter was dissolved in toluene (100 mL), and the solution was treated with iodine (6.4 g, 25.2 mmol), triphenylphosphine (7.1 g, 27.0 mmol), and imidazole (3.7 g, 54.3 mmol) and heated for 1.5 h at 80 °C. The reaction mixture was then cooled to rt, the supernatant phase was removed by decantation, and the pasty white residue was taken up in ether and water. The excess iodine was destroyed by addition of sodium thiosulfate pentahydrate to the biphasic mixture, and the phases were separated. The organic phases were combined and dried over Na_2SO_4, and the solvents were removed under vacuum. The residue was triturated with ether, and the resulting precipitate of triphenylphosphine oxide was removed by filtration through Celite. The filtrate was purified by column chromatography on silica gel (heptane followed by heptane−ethyl acetate 9:1), affording compound **12** (4.6 g, 78%) as a colorless oil: $[\alpha]^{25}_D$ +74.9 (*c* 2.0, CH_3OH); ^1H NMR (250 MHz, $CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3H), 1.33 (s, 3H), 1.46 (s, 3H), 3.28 (dd, J = 6.6, 9.6 Hz, 1H), 3.36 (dd, J = 7.6, 9.6 Hz, 1H), 3.47 (oct, J = 7.1, 9.7 Hz, 1H), 3.72 (oct, J = 7.1, 9.7 Hz, 1H), 4.20 (dt, J = 3.5, 7.0 Hz, 1H), 4.61 (d, J = 5.8 Hz, 1H), 4.77 (dd, J = 3.5, 5.8 Hz, 1H), 5.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 15.6, 25.6, 25.7, 63.4, 80.1, 81.1, 85.9, 106.5, 113.2; mass spectrum (HRCI) calcd for $C_{10}H_{18}IO_4$ [$M + 1^+$] *m*/*z* 329.0251, found *m*/*z* 329.0279.

Ethyl 5-Deoxy-5-*C*-(diethoxyphosphinyl)-2,3-*O*-isopropylidene-α-D-lyxofuranoside (13). A solution of compound **12** (9.19 g, 28.0 mmol) in triethyl phosphite (18 mL, freshly distilled over sodium) was heated at 160 °C under a constant stream of nitrogen for 30 h, additional triethylphosphite being added to the reaction mixture after 6 h (6 mL) and 21 h (2 mL) of heating. At the end of the reaction period, the excess triethyl phosphite was removed by distillation under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate−heptane 3:1 followed by 4:1 followed by ethyl acetate), affording compound **13** (8.10 g, 85%) as a colorless oil: $[\alpha]^{22}_D$ +40.2 (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.19 (t, J = 7.0 Hz, 3H), 1.31 (s, 3H), 1.33 (t, J = 7.0 Hz, 6H), 1.45 (s, 3H), 2.19 (ddd, J(H,H) = 6.6, 15.3 Hz, J(H,P) = 18.0 Hz, 1H), 2.32 (ddd, J(H,H) = 6.6, 15.3 Hz, J(H,P) = 18.0 Hz, 1H), 3.45 (dq, J = 7.0, 9.7 Hz, 1H), 3.71 (dq, J = 7.0, 9.7 Hz, 1H), 4.14 (m, 4H), 4.29 (pseudo dq, J = 3.5, 6.8 Hz, 1H), 4.56 (d, J = 5.8 Hz, 1H), 4.68 (dd, J = 5.8, 3.5 Hz, 1H), 4.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 16.3, 16.4, 25.0, 25.5 (d, J(C,P) = 140.0 Hz), 26.1, 61.5, 61.9 (2 × d, J(C,P) = 6.0 Hz), 62.7, 74.6, 80.4 (d, J(C,P) = 6.6 Hz), 85.2, 105.6, 112.4; IR (film) 1250, 1025, 970 cm^{-1}; mass spectrum (CI) *m*/*z* 339 [$M + 1^+$]. Anal. Calcd for $C_{14}H_{27}O_7P$: C, 49.70; H, 8.04; P, 9.15. Found: C, 49.43; H, 7.98; P, 9.36.

Ethyl 5-Deoxy-5-*C*-(diethoxyphosphinyl)-α-D-lyxofuranoside (10). A solution of acetonide **13** (3.05 g, 9.0 mmol) in absolute ethanol (300 mL) was refluxed in the presence of iodine (1.60 g, 6.3 mmol). After 3 h, more iodine (700 mg, 2.7 mmol) was added to the reaction mixture, and the latter was refluxed for an additional 10 h. The solution was then cooled, sodium thiosulfate pentahydrate (4.50 g, 18.0 mmol) was added, and the solvent was removed under vacuum. The solid residue was dissolved in ethyl acetate (150 mL), and the solution was washed with saturated aqueous NaCl (50 mL). The aqueous phase was in turn extracted with ethyl acetate (2 × 200 mL), and the organic phases were combined, dried

over Na_2SO_4, and evaporated under vacuum. The oily residue was purified by chromatography on silica gel (ethyl acetate−ethanol, 99:1 followed by 98:2 followed by 95:5), providing starting material **13** (1.20 g, 40%) followed by the diol **10** (1.08 g, 40%), obtained as a colorless oil: $[\alpha]^{22}_D$ +36.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.0 Hz, 6H), 2.21 (ddd, J(H,H) = 5.5, 15.2 Hz, J(H,P) = 18.7 Hz, 1H), 2.33 (ddd, J(H,H) = 7.3, 15.2 Hz, J(H,P) = 18.7 Hz, 1H), 3.48 (dq, J = 7.0, 9.5 Hz, 1H), 3.71 (dq, J = 7.0, 9.5 Hz, 1H), 4.00 (d, J = 7.0 Hz, 1H, exchangeable with D_2O), 4.13 (m, 5H), 4.34 (m, 1H), 4.40 (m, 1H), 4.53 (d, J = 4.8 Hz, 1H, exchangeable with D_2O), 4.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 16.5, 16.6, 26.5 (d, J(C,P) = 140.0 Hz), 62.3 and 62.5 (2 × d, J(C,P) = 6.7 Hz), 63.8, 71.5 (d, J(C,P) = 4.0 Hz), 75.1, 77.0, 107.6; IR (film) 3380, 1220, 1030, 970 cm^{-1}; mass spectrum (CI) m/z 299 [M + 1$^+$]. Anal. Calcd for $C_{11}H_{23}O_7P$: C, 44.30; H, 7.77; P, 10.38. Found: C, 44.13; H, 7.84; P, 9.98.

Ethyl 5-Deoxy-5-*C*-(diethoxyphosphinyl)-2,3-*O*-sulfinyl-α-D-lyxofuranoside (14). To a solution of diol **10** (2.65 g, 8.88 mmol) and triethylamine (5.0 mL, 35.5 mmol) in THF (100 mL) held at −25 °C was added dropwise over 15 min a solution of freshly distilled thionyl chloride (1.3 mL, 17.8 mmol) in THF (5 mL). After completion of the addition, the reaction mixture was stirred for 15 min at −25 °C and then diluted with ethyl acetate (100 mL). Saturated aqueous NaCl solution (100 mL) was added, the phases were separated, and the organic phase was washed with saturated aqueous NaCl solution (100 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed under vacuum, leaving crude **14** (3.03 g, 98%) as an oil that was used in the following step without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 1.35 (t, J = 7.0 Hz, 6H), 2.29 (m, 2H), 3.51 (m, 1H), 3.75 (m, 1H), 4.15 (m, 4H), 4.54 (m, 1H), 5.07 (d, J = 5.3 Hz, 0.5 H), 5.08 (s, 0.5 H), 5.25 (d, J = 6.1 Hz, 0.5 H), 5.27 (s, 0.5 H), 5.33 (dd, J = 6.1, 3.6 Hz, 0.5 H), 5.46 (dd, J = 5.6, 3.6 Hz, 0.5 H); IR (film) 1250, 1220, 1025, 970 cm^{-1}; mass spectrum (CI) m/z 345 [M + 1$^+$].

Ethyl 5-Deoxy-5-*C*-(diethoxyphosphinyl)-α-D-lyxofuranoside 2,3-Sulfate (15). A vigorously stirring solution of sulfite **14** (3.0 g, 8.7 mmol) in acetonitrile (18 mL), carbon tetrachloride (18 mL), and water (27 mL) was treated with ruthenium trichloride hydrate (91 mg, 0.44 mmol) and sodium metaperiodate (3.80 g, 17.8 mmol) for 2.5 h at rt. The reaction mixture was diluted with water (60 mL) and extracted with dichloromethane (3 × 100 mL), and the combined organic extracts were dried over Na_2SO_4. The residue left after removal of the solvents *in vacuo* was purified by flash chromatography on silica gel (ethyl acetate), affording **15** (2.70 g, 86%) as a pale yellow oil: $[\alpha]^{22}_D$ +34.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 1.35 (t, J = 7.0 Hz, 6H), 2.30 (dd, J(H,H) = 7.0 Hz, J(H,P) = 18.6 Hz, 2H), 3.53 (dq, J = 7.0, 9.6 Hz, 1H), 3.76 (dq, J = 7.0, 9.6 Hz, 1H), 4.15 (m, 4H), 4.54 (dq, J(H,H) = 3.3, 7.1 Hz, J(H,P) = 7.1 Hz, 1H), 5.14 (d, J = 6.0 Hz, 1H), 5.24 (s, 1H), 5.38 (dd, J = 6.0, 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 16.3, 16.4, 25.2 (d, J(C,P) = 140.0 Hz), 62.1 and 62.4 (2 × d, J(C,P) = 6.5 Hz), 63.6, 74.1, 83.6 (d, J(C,P) = 6.7 Hz), 86.3, 103.3; IR (film) 1397, 1230, 1213, 1030, 970 cm^{-1}; mass spectrum (CI) m/z 361 [M + 1$^+$]. Anal. Calcd for $C_{11}H_{21}O_9PS$: C, 36.67; H, 5.87; P, 8.60; S, 8.90. Found: C, 36.81; H, 6.02; P, 8.89; S, 8.64.

Ethyl 3-Azido-3,5-dideoxy-5-*C*-(diethoxyphosphinyl)-α-D-arabinofuranoside (16). A solution of compound **15** (3.20 g, 8.9 mmol) in DMF (45 mL) was heated at 60 °C for 2.5 h in the presence of sodium azide (1.16 g, 17.8 mmol). The solvent was removed *in vacuo*, the solid residue was taken up in THF (45 mL), and concentrated sulfuric acid (478 μL, 8.9 mmol) followed by water (160 μL, 8.9 mmol) were added. The solution was stirred for 2 h at rt, and after neutralization by addition of saturated aqueous sodium hydrogen carbonate, it was extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were dried over Na_2SO_4, the solvents were removed under vacuum, and the residue was purified by chromatography on silica gel (ethyl acetate−heptane 3:1 followed by ethyl acetate), affording compound **16** (2.74 g, 95%) as a colorless oil: $[\alpha]^{22}_D$ +70.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 1.34 (2 × t, J = 7.0 Hz, 6H), 2.24 (ddd, J(H,H) = 4.0, 15.4 Hz, J(H,P) = 17.5 Hz, 1H), 2.38 (ddd, J(H,H) = 6.2, 15.4 Hz, J(H,P) = 18.5 Hz, 1H), 3.49 (dq, J = 7.0, 9.4 Hz, 1H), 3.72 (dq, J = 7.0, 9.4 Hz, 1H), 3.85 (d, J = 5.4 Hz, 1H), 4.13 (m, 5H), 4.24 (pseudo q, J = 7.0 Hz, 1H), 4.99 (s, 1H), 5.23 (m, 1H, exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 16.3, 16.4, 30.0 (d, J(C,P) = 140.0 Hz), 61.8 and 62.5 (2 × d, J(C,P) = 6.7 Hz), 63.0, 70.7 (d, J(C,P) = 4.5 Hz), 76.9, 80.9, 107.9; IR (film) 3340, 2110, 1250, 1030, 970 cm^{-1}; mass spectrum (CI) m/z 324 [M + 1$^+$]. Anal. Calcd for $C_{11}H_{22}N_3O_6P$: C, 40.85; H, 6.86; N, 13.00; P, 9.59. Found: C, 41.15; H, 6.95; N, 12.85; P, 9.36.

Ethyl 3-Azido-3,5-dideoxy-5-*C*-(diethoxyphosphinyl)-2-*O*-tosyl-α-D-arabinofuranoside (17). A solution of compound **16** (2.49 g, 7.7 mmol) and *p*-toluenesulfonyl chloride (5.15 g, 27.0 mmol) in anhydrous pyridine (45 mL) was stirred for 90 h at 20 °C under nitrogen. The reaction mixture was concentrated under vacuum, and the residue was partitioned between ethyl acetate (150 mL) and water (150 mL). The phases were separated, and the organic phase was dried over Na_2SO_4. Evaporation of the solvent left the crude product, which was purified by chromatography on silica gel (heptane−ethyl acetate 1:2), affording pure **17** (3.52 g, 95%) as a colorless oil: $[\alpha]^{22}_D$ +59.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (t, J = 7.0 Hz, 3H), 1.33 (t, J = 7.0 Hz, 6H), 2.11 (ddd, J(H,H) = 6.7, 15.1 Hz, J(H,P) = 18.7 Hz, 1H), 2.21 (ddd, J(H,H) = 6.7, 15.1 Hz, J(H,P) = 18.4 Hz, 1H), 2.47 (s, 3H), 3.37 (dq, J = 7.0, 9.6 Hz, 1H), 3.66 (dq, J = 7.0, 9.6 Hz, 1H), 3.80 (dd, J = 2.5, 6.6 Hz, 1H), 4.12 (m, 5H), 4.66 (d, J = 2.5 Hz, 1H), 4.98 (s, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 16.3, 16.4, 21.7, 30.3 (d, J(C,P) = 140.0 Hz), 61.9 and 62.1 (2 × d, J(C,P) = 6.5 Hz), 63.3, 69.3 (d, J(C,P) = 9.7 Hz), 76.3, 87.7, 104.3, 128.1, 130.2, 132.6, 145.7; IR (film) 2113, 1372, 1192, 1180, 1253, 1029, 965 cm^{-1}; mass spectrum (CI) m/z 478 [M + 1$^+$]. Anal. Calcd for $C_{18}H_{28}N_3O_8PS$: C, 45.28; H, 5.91; N, 8.80; P, 6.49; S, 6.71. Found: C, 45.07; H, 5.71; N, 8.72; P, 6.23; S, 6.66.

3-Azido-3,5-dideoxy-5-*C*-(diethoxyphosphinyl)-2-*O*-tosyl-α,β-D-arabinofuranose (18). A solution of the furanoside **17** (3.78 g, 7.9 mmol) in trifluoroacetic acid and water (80 mL of a 9:1 mixture) was heated at 50 °C for 54 h. The reaction mixture was evaporated to dryness under vacuum, the residue was redissolved in trifluoroacetic acid and water (9:1, 80 mL), and the solution was heated for a further 54 h at 50 °C. The solvents were again removed under vacuum, the residue was dissolved in ethyl acetate (100 mL), and the solution was washed with aqueous sodium carbonate (50 mL of a 5% solution). The aqueous phase was extracted with ethyl acetate (2 × 50 mL), the organic phases were combined and dried over Na_2SO_4, and the solvent was removed under vacuum, affording crude **18** (3.55 g) that was used in the following step without further purification. An analytical sample of **18** was obtained by chromatography of the crude material on silica gel (heptane−ethyl acetate 1:3): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.32 and 1.33 (2 × t, J = 7.0 Hz, 6H), 2.10−2.34 (m, 2H), 2.47 (s, 3H), 3.86 (dd, J = 2.4, 6.2 Hz, 0.65 H), 3.96 (m, 0.35 H), 4.12 (m, 4H), 4.31 (dd, J = 8.1, 6.5 Hz, 0.35 H), 4.33 (m, 0.65 H), 4.57 (dd, J = 4.2, 8.2 Hz, 0.35 H), 4.66 (d, J = 2.4 Hz, 0.65 H), 4.93 (m, 0.65 H, exchangeable with D_2O), 5.25 (m, 0.35 H), 5.37 (s, 0.65 H), 5.42 (m, 0.35 H, exchangeable with D_2O), 7.38 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 16.4, 21.7, 30.4, 32.2 (2 × d, J(C,P) = 140.0 Hz), 62.2 and 62.5 (2 × d, J(C,P) = 6.0 Hz), 66.1 and 69.5 (2 × d, J(C,P) = 10.0 Hz), 74.5, 76.3, 81.9, 87.9, 94.6, 99.8, 128.1, 130.0, 130.2, 132.5, 145.7; IR (film) 3260, 2115, 1368, 1190, 1180, 1220, 1030, 975 cm^{-1}; mass spectrum (CI) m/z 450 [M + 1$^+$]. Anal. Calcd for $C_{16}H_{24}N_3O_8PS$: C, 42.76; H, 5.38; N, 9.35; P, 6.89; S, 7.13. Found: C, 42.92; H, 5.38; N, 9.34; P, 6.71; S, 7.03.

***tert*-Butyldimethylsilyl 3-Azido-3,5-dideoxy-5-*C*-(diethoxyphosphinyl)-2-*O*-tosyl-α,β-D-arabinofuranoside (19).** To a solution of compound **18** (3.5 g, 7.8 mmol) in DMF (16 mL) held under nitrogen was added successively imidazole (1.08 g, 15.8 mmol) and *tert*-butyldimethylsilyl chloride (1.80 g, 11.95 mmol). The reaction mixture was stirred for 24 h at

rt. The solvent was then removed under reduced pressure, the residue was dissolved in ethyl acetate (60 mL), and the solution was washed with water (40 mL). The organic phase was dried over Na_2SO_4, the solvent was removed *in vacuo*, and the resulting crude product was purified by chromatography on silica gel (heptane−ethyl acetate 2:3 followed by 1:2) providing **19** (3.65 g, 82%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.04, 0.07, 0.13, and 0.15 (4 × s, 6 H), 0.84 (s, 5.4 H), 0.92 (s, 3.6 H), 1.32 (t, J = 7.0 Hz, 6 H), 2.00−2.32 (m, 2H), 2.46 (s, 3H), 3.75 (dd, J = 1.6, 6.0 Hz, 0.6 H), 3.95 (m, 0.4 H), 4.12 (m, 4.4 H), 4.23 (m, 0.6 H), 4.41 (dd, J = 3.8, 8.1 Hz, 0.4 H), 4.59 (d, J = 1.9 Hz, 0.6 H), 5.28 (s, 0.6 H), 5.32 (d, J = 3.8 Hz, 0.4 H), 7.38 (2 × d, J = 8.2 Hz, 2H), 7.83 (2 × d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, −4.5, 16.3, 16.4, 17.8, 17.9, 21.7, 25.5, 25.6, 30.7, and 34.1 (2 × d, J(C,P) = 139.0 Hz), 61.8, 62.0, and 62.1 (3 × d, J(C,P) = 5.0 Hz), 66.8 and 69.2 (2 × d, J(C,P) = 8.0 Hz), 75.2, 76.7, 82.3, 88.9, 95.0, 100.0, 128.0, 128.1, 130.0, 130.2, 132.7, 132.8, 145.5, 145.7; IR (film) 2110, 1372, 1195, 1181, 1256, 1032, 965 cm^{-1}; mass spectrum (CI) m/z 564 [M + 1$^+$]. Anal. Calcd for $C_{22}H_{38}N_3O_8PSSi$: C, 46.88; H, 6.80; N, 7.45; P, 5.49; S, 5.69; Si, 4.97. Found: C, 46.69; H, 6.68; N, 7.41; P, 5.57; S, 5.89; Si, 5.27.

***tert*-Butyldimethylsilyl 2,3-Aziridino-5-*C*-(diethoxyphosphinyl)-2,3,5-trideoxy-α,β-D-ribofuranoside (20).** A solution of compound **19** (3.65 g, 6.48 mmol) in methanol (40 mL) was hydrogenated for 2.5 h at atmospheric pressure in the presence of 10% palladium on carbon (450 mg). The reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The oily residue was then dissolved in DMF (65 mL) and diethylamine (7.5 mL), and the solution was heated at 105 °C for 6 h. After removal of the solvents under reduced pressure, the remaining crude material was purified by chromatography on silica gel (dichloromethane−ethanol 95:5), affording aziridine **20** (1.75 g, 74%) as a reddish oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.12 and 0.13 (2 × s, 6H), 0.91 (s, 9H), 1.33 (t, J = 7.0 Hz, 6H), 1.95 (ddd, J(H,H) = 7.8, 15.1 Hz, J(H,P) = 18.6 Hz, 0.7 H), 1.97 (m, 0.3 H), 2.09 (ddd, J(H,H) = 6.0, 15.1 Hz, J(H,P) = 19.2 Hz, 0.7 H), 2.12 (m, 0.3 H), 2.65 (d, J = 2.9 Hz, 1H), 2.74 (d, J = 3.4 Hz, 0.7 H), 3.03 (m, 0.3 H), 4.13 (m, 4H), 4.30 (m, 0.3 H), 4.43 (pseudo dt, J(H,H) = 6.0, 8.0 Hz, J(H,P)= 8.0 Hz, 0.7 H), 5.29 (d, J = 2.0 Hz, 0.3 H), 5.54 (s, 0.7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, 16.4, 16.5, 18.0, 25.7, 31.7 (d, J(C,P) = 137.0 Hz), 38.4, 39.1 (d, J(C,P) = 9.5 Hz), 61.8 (d, J(C,P) = 6.7 Hz), 73.8, 97.3; IR (film) 3280, 1253, 1150, 1025, 965 cm^{-1}; mass spectrum (HRCI) calcd for $C_{15}H_{33}NO_5PSi$ [M + 1$^+$] m/z 366.1865, found m/z 366.1863.

***tert*-Butyldimethylsilyl 2,3-[*N*-(Benzyloxycarbonyl)-aziridino]-5-*C*-(diethoxyphosphinyl)-2,3,5-trideoxy-α,β-D-ribofuranoside (21).** To a solution of aziridine **20** (1.75 g, 4.79 mmol) and triethylamine (1.68 mL, 12.0 mmol) in DMF (20 mL) was added at 0 °C under nitrogen a solution of benzyl chloroformate (1.37 mL, 9.6 mmol) in DMF (2 mL). The reaction mixture was stirred for 30 min at 0 °C and then for 3 h at rt. The solution was diluted with ethyl acetate (40 mL) and washed with water (25 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under vacuum, and the residue was purified by chromatography on silica gel (heptane−ethyl acetate 1:2 followed by 1:3), affording compound **21** (1.93 g, 81%) as a colorless oil. The α- and β-anomers could be separated by careful preparative TLC of an aliquot of the mixture (20 mg; heptane−ethyl acetate 1:3; silica gel), the faster migrating component corresponding to the α-anomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.90 (s, 9H), 1.32 (t, J = 7.0 Hz, 6H), 1.95 (ddd, J(H,H)= 8.3, 15.2 Hz, J(H,P) = 18.4 Hz, 1H), 2.08 (ddd, J(H,H) = 5.6, 15.2 Hz, J(H,P) = 19.5 Hz, 1H), 3.31 (dd, J = 1.2, 4.6 Hz, 1H), 3.44 (d, J = 4.6 Hz, 1H), 4.11 (m, 4H), 4.61 (ddd, J(H,H) = 8.3, 5.6 Hz, J(H,P) = 10.2 Hz, 1H), 5.10 (d, J = 12.3 Hz, 1H), 5.16 (d, J = 12.3 Hz, 1H), 5.50 (d, J = 1.2 Hz, 1H), 7.35 (br s, 5H). β-anomer δ = 0.09 (2 × s, 6H), 0.87 (s, 9H), 1.31 (t, J = 7.0 Hz, 6H), 2.15 (m, 1H), 2.26 (m, 1H), 3.14 (d, J = 3.5 Hz, 1H), 3.55 (d, J = 3.5 Hz, 1H), 4.11 (m, 4H), 4.55 (m, 1H), 5.19 (2 × d, J = 12.1 Hz, 2H), 5.38 (s, 1H), 7.35 (br s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) α- and β-anomer δ −4.9, −4.4, −4.2, 16.3, 16.4, 16.5, 17.8, 18.2, 25.6, 25.8, 30.7, and 31.9 (2 × d, J(C,P) = 138.0 Hz), 42.8 and 44.5 (2 × d, J(C,P) = 7.8, 4.2 Hz), 44.3, 44.6, 61.9, 62.0, and 62.1 (3 × d, J(C,P) = 6.5 Hz), 68.1, 68.3, 71.7, 72.3, 95.8, 96.3, 128.2, 128.3, 128.4, 128.5, 135.5, 135.6, 159.5, 161.3; IR (film) 1727, 1257, 1162, 1025, 965 cm^{-1}; mass spectrum (CI) m/z 500 [M + 1$^+$]. Anal. Calcd for $C_{23}H_{38}NO_7PSi$: C, 55.29; H, 7.67; N, 2.80; P, 6.20. Found: C, 55.41; H, 7.51; N, 2.74; P, 6.07.

2,3-[*N*-(Benzyloxycarbonyl)aziridino]-5-*C*-(diethoxyphosphinyl)-2,3,5-trideoxy-α,β-D-ribofuranose (22). A solution of compound **21** (800 mg, 1.6 mmol) in dichloromethane (18 mL) was treated at −60 °C under nitrogen with tetrabutylammonium fluoride trihydrate (555 mg, 1.76 mmol). The reaction mixture was slowly allowed to come to rt over 90 min, after which time the solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (ethyl acetate) affording compound **22** (535 mg, 87%) as a white solid that was crystallized from ethyl acetate: mp 131−132 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 6H), 2.18 (ddd, J(H,H) = 6.4, 15.2 Hz, J(H,P) = 18.6 Hz, 1H), 2.34 (ddd, J(H,H) = 7.4, 15.2 Hz, J(H,P) = 18.8 Hz, 1H), 3.27 (d, J = 3.5 Hz, 1H), 3.34 (d, J = 3.5 Hz, 1H), 4.10 (m, 4H), 4.57 (pseudo dt, J(H,H) = 6.9 Hz, J(H,P) = 10.3 Hz, 1H), 5.11 (2 × d, J = 12.1 Hz, 2H), 5.49 (s, 1H), 5.80 (m, 1H, exchangeable with D_2O), 7.34 (s, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 16.4, 16.5, 31.5 (d, J(C,P) = 138.0 Hz), 43.0 (d, J(C,P) = 13.0 Hz), 44.0, 61.0 and 62.4 (2 × d, J(C,P) = 7.0 Hz), 68.3, 71.2, 95.7, 128.3, 128.4, 128.6, 135.6, 159.6; IR (film) 3250, 1727, 1257, 975 cm^{-1}; mass spectrum (CI) m/z 386 [M + 1$^+$]. Anal. Calcd for $C_{17}H_{24}NO_7P$: C, 52.99; H, 6.28; N, 3.63; P, 8.04. Found: C, 52.92; H, 6.31; N, 3.59; P, 8.15.

(1*R*,4*S*,5*S*)-*N*-(Benzyloxycarbonyl)-4-[(diethoxyphosphinyl)methyl]-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (23). A solution of compound **22** (535 mg, 1.39 mmol) in acetonitrile (18 mL) was treated at 20 °C under nitrogen with 4-methylmorpholine *N*-oxide (245 mg, 2.09 mmol), finely powdered 4 Å molecular sieves (695 mg), and tetrapropylammonium perruthenate (59 mg, 0.168 mmol). The reaction mixture was stirred for 3 h, after which time it was concentrated under reduced pressure. The residue was taken up in ethyl acetate, and the mixture was filtered through a pad of silica gel, affording, after removal of the solvent *in vacuo*, compound **23** (460 mg, 86%) as a colorless oil. An analytically pure sample of **23** was obtained by chromatography of an aliquot on silica gel using ethyl acetate as eluent: $[\alpha]^{22}_D$ −13.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (t, J = 7.0 Hz, 6H), 2.18 (ddd, J(H,H) = 7.8, 15.4 Hz, J(H,P) = 18.1 Hz, 1H), 2.29 (ddd, J(H,H) = 4.9, 15.4 Hz, J(H,P) = 19.7 Hz, 1H), 3.49 (d, J = 3.3 Hz, 1H), 3.88 (d, J = 3.3 Hz, 1H), 4.12 (m, 4H), 4.95 (ddd, J(H,H) = 5.1, 7.8 Hz, J(H,P) = 15.1 Hz, 1H), 5.16 (2 × d, J = 12.1 Hz, 2H), 7.35 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 16.4, 30.3 (d, J(C,P) = 141.0 Hz), 37.8, 44.0 (d, J(C,P) = 7.0 Hz), 62.4 and 62.5 (2 × d, J(C,P) = 5.5 Hz), 69.3, 72.7, 128.2, 128.5, 128.7, 134.6, 158.1, 168.2; IR (film) 1800, 1731, 1257, 1025, 970 cm^{-1}; mass spectrum (CI) m/z 384 [M + 1$^+$]. Anal. Calcd for $C_{17}H_{22}NO_7P$: C, 53.27; H, 5.78; N, 3.65; P, 8.08. Found: C, 53.55; H, 5.87; N, 3.66; P, 7.79.

3-[*N*-(Benzyloxycarbonyl)amino]-5-*C*-(diethoxyphosphinyl)-2-(ethylthio)-2,3,5-trideoxy-D-arabino-1,4-lactone (24). To a solution of compound **23** (64 mg, 0.167 mmol) in ethanethiol (2 mL) was added at 20 °C under nitrogen boron trifluoride etherate (45 μL, 0.366 mmol). The reaction mixture was stirred for 3 h and then diluted with ethyl acetate (5 mL) and neutralized by addition of aqueous sodium hydrogen carbonate (2 mL of a 0.5 M solution). The phases were separated, the aqueous phase was extracted with ethyl acetate (2 × 5 mL), and the combined organic phases were dried over Na_2SO_4. Removal of the solvents under reduced pressure and chromatography of the residue on silica gel (ethyl acetate) provided compound **24** (65 mg, 87%) as a colorless oil: $[\alpha]^{22}_D$ −12.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 6H), 2.29 (dd, J(H,H) = 6.5 Hz, J(H,P) = 18.5 Hz, 2H), 2.77 (q, J = 7.3 Hz, 2H), 3.87 (d, J = 8.3 Hz, 1H), 4.04 (m, 5H), 4.66 (m, 1H), 5.10 (2 × d, J = 12.2 Hz, 2H), 6.74 (d, J = 7.7 Hz, 1H, exchangeable with D_2O), 7.34 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 16.2, 16.3, 25.5, 30.2 (d, J(C,P) = 140.0 Hz), 46.3, 59.3 (d, J(C,P) = 13.0 Hz),

62.1 and 62.7 (2 × d, J(C,P) = 6.0 Hz), 67.1, 76.9, 128.2, 128.3, 128.5, 156.1, 172.3; IR (film) 3280, 1793, 1720, 1539, 1230, 1030, 970 cm^{-1}; mass spectrum (CI) m/z 466 [M + 1^+]. Anal. Calcd for $C_{19}H_{28}NO_7PS$: C, 51.23; H, 6.34; N, 3.14; P, 6.96; S, 7.20. Found: C, 51.11; H, 6.28; N, 2.98; P, 6.96; S, 7.08.

2-[*N*-(Benzyloxycarbonyl)amino]-2,5-dideoxy-5-*C*-(diethoxyphosphinyl)-D-ribono-1,4-lactone (25). A solution of aziridine **23** (50 mg, 0.13 mmol) in absolute ethanol (5 mL) was treated at 5 °C under nitrogen with boron trifluoride etherate (34 μL, 0.27 mmol). The reaction mixture was stirred for 30 min at 5 °C and for 5 h at 60 °C, after which time it was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), and the solution was neutralized by addition of aqueous sodium hydrogen carbonate (5 mL of a 0.5 M solution). 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. Evaporation of the solvent under reduced pressure left a crude product that was purified by chromatography on silica gel, providing pure compound **25** (21 mg, 40%) as a colorless oil: $[\alpha]^{26}_D$ +26.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 6H), 2.22 (ddd, J(H,H) = 6.3, 15.3 Hz, J(H,P) = 19.3 Hz, 1H), 2.49 (ddd, J(H,H) = 7.7, 15.3 Hz, J(H,P) = 18.4 Hz, 1H), 4.12 (m, 5H), 4.61 (pseudo t, J = 6.3 Hz, 1H), 4.99−5.08 (m, 2H, partly exchangeable with D_2O), 5.12 (s, 2H), 5.77 (d, J = 5.5 Hz, exchangeable with D_2O, 1H), 7.35 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 16.4, 26.2 (d, J(C,P) = 140.0 Hz), 57.9, 62.7 (d, J(C,P) = 7.0 Hz), 67.7, 73.1 (d, J(C,P) = 6.0 Hz), 76.7, 128.2, 128.4, 128.6, 171.9; IR (film) 3300, 1790, 1715, 1540, 1220, 1025 cm^{-1}; mass spectrum (CI) m/z 402 [M + 1^+]. Anal. Calcd for $C_{17}H_{24}NO_8P$: C, 50.87; H, 6.03; N, 3.49. Found: C, 50.82; H, 6.03; N, 3.35.

2-[*N*-(Benzyloxycarbonyl)amino]-2,5-dideoxy-5-*C*-(dimethoxyphosphinyl)-D-ribono-1,4-lactone (26). A solution of aziridine **23** (77 mg, 0.20 mmol) in anhydrous methanol (6 mL) was heated at 50 °C for 5 h in the presence of boron trifluoride etherate (54 μL, 0.44 mmol). The reaction mixture was then evaporated to dryness under reduced pressure, the residue was dissolved in ethyl acetate (5 mL), and the solution was neutralized with aqueous sodium hydrogen carbonate (2 mL of a 0.5 M solution). 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. Evaporation of the solvent under reduced pressure and chromatography of the residue on silica gel (ethyl acetate followed by ethyl acetate−ethanol 95:5) afforded compound **26** (25 mg, 33%) as a colorless oil contaminated with ∼5% (by ^{1}H NMR) of the diethoxyphosphinyl and ethoxymethoxyphosphinyl derivatives: $[\alpha]^{26}_D$ +29.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (ddd, J(H,H) = 6.7, 15.5 Hz, J(H,P) = 18.9 Hz, 1H), 2.53 (ddd, J(H,H) = 7.0, 15.5 Hz, J(H,P) = 18.5 Hz, 1H), 3.75 (2 × d, J = 11.0 Hz, 6H), 4.15 (pseudo t, J = 6.1 Hz, 1H), 4.59 (pseudo t, J = 6.5 Hz, 1H), 4.95−5.10 (m, 2H, partly exchangeable with D_2O), 5.11 (s, 2H), 5.95 (d, J = 5.4 Hz, 1H, exchangeable with D_2O), 7.35 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2 (d, J(C,P) = 140.0 Hz), 52.9 and 53.0 (2 × d, J(C,P) = 4.6, 6.5 Hz), 57.7, 67.7, 72.9, 76.5, 128.2, 128.4, 128.6, 135.6, 171.9; IR (film) 3310, 1790, 1715, 1535, 1260, 1030 cm^{-1}; mass spectrum (CI) m/z 374 [M + 1^+].

3-*O*-Acetyl-2-[*N*-(benzyloxycarbonyl)amino]-2,5-dideoxy-5-*C*-(dimethoxyphosphinyl)-D-ribono-1,4-lactone (27) and (5*S*)-3-[*N*-(Benzyloxycarbonyl)amino]-5-(dimethoxyphosphinyl)-2(5*H*)-furanone (28). A solution of compound **26** (19 mg, 0.05 mmol) in pyridine (1 mL) and acetic anhydride (0.2 mL) was left standing overnight at 4 °C. The reaction mixture was evaporated to dryness under reduced pressure (bath temperature < 25 °C), leaving compound **27** (20 mg, 100%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.22 (dd, J(H,H) = 6.7 Hz, J(H,P) = 19.2 Hz, 2H), 3.72 (2 × d, J = 11.2 Hz, 6H), 4.28 (dd, J = 4.9, 7.8 Hz, 1H), 5.11 (s, 2H), 5.21 (m, 1H), 5.45 (pseudo t, 1H), 6.39 (d, J = 7.8 Hz, 1H, exchangeable with D_2O), 7.33 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 25.8 (d, J(C,P) = 144.0 Hz), 52.7 and 53.0 (2 × d, J(C,P) = 6.5 Hz), 56.1, 67.8, 74.1 (d, J(C,P) = 9.0 Hz), 74.8, 128.3, 128.5, 128.7, 135.9, 169.8, 171.1; IR (film) 3250, 1795, 1740, 1720, 1540, 1225, 1030 cm^{-1}; mass spectrum (CI) m/z 356 [M − CH_3CO_2H + 1^+].

Chromatography of compound **27** on silica gel (ethyl acetate) gave exclusively the elimination product **28** (14 mg, 78%) also as a colorless oil: $[\alpha]^{26}_D$ +8.1 (*c* 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (ddd, J(H,H) = 7.3, 15.2 Hz, J(H,P) = 18.3 Hz, 1H), 2.33 (ddd, J(H,H) = 6.6, 15.2 Hz, J(H,P) = 18.3 Hz, 1H), 3.78 (d, J = 11.0 Hz, 3H), 3.81 (d, J = 11.0 Hz, 3H), 5.21 (s, 2H), 5.32 (pseudo q, J = 7.2 Hz, 1H), 7.02 (m, 1H), 7.22 (m, 1H), 7.38 (s, 5H); IR (film) 3210, 1768, 1730, 1660, 1545, 1218, 1025 cm^{-1}; mass spectrum (CI) m/z 356 [M + 1^+]. Anal. Calcd for $C_{15}H_{18}NO_7P$: C, 50.71; H, 5.11; N, 3.94. Found: C, 50.69; H, 5.31; N, 3.68.

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 suggestions and encouragement.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **23** and **25**−**27** and an ^{1}H NMR spectrum of compound **28** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9623494