Reactivity of 2,3-Aziridino-2,3-dideoxy-D-lyxono-γ-lactone Derivatives, Rigid Analogues of Aziridine-2-carboxylic Esters, toward Soft and Hard Nucleophiles: Control of Lactone vs Aziridine Ring Opening and C-2 vs C-3 Regioselectivity

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The reactivities of (1*S*,4*S*,5*R*)-*N*-acetyl-4-(methoxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**2**) and its N-Cbz analogue **12** toward soft nucleophiles (thiols, acetic acid, bromide) and hard nucleophiles (alcohols, benzylamine) were studied and compared to the reported reactivities of aziridine-2-carboxylic esters (**1**) with the same nucleophiles. Both **2** and **12** reacted with soft nucleophiles in the presence of a Lewis acid to give the products of aziridine ring opening at C-2. This regioselectivity is in distinct contrast to the known reactions of **1** with these nucleophiles wherein aziridine ring opening at C-3 is almost always observed. The Lewis acid-catalyzed reaction of **2** with alcohols (methanol or benzyl alcohol) gave products arising from initial attack of the lactone ring yielding the corresponding methyl or benzyl esters, respectively. These intermediates further reacted to give, in the case of methanol, exclusively the product of N-deacetylation, that is, aziridine-2-carboxylic methyl ester **20** or, in the case of benzyl alcohol, a mixture of the N-deacetylated aziridine-2-carboxylic benzyl esters **17** and **18**, the results of both lactone ring opening and aziridine ring opening at C-3. The latter compound spontaneously cyclized to its lactone form **19** during the course of its purification. N-Deacetylation by alcohols could be suppressed by using the N-Cbz aziridine derivative **12** as starting material. Thus, **12** reacted with methanol or benzyl alcohol in the presence of a Lewis acid to give lactones **21** and **22**, respectively, the products of aziridine ring opening at C-3. The intermediacy of an aziridine-2-carboxylic ester derivative in these reactions, via initial opening of the lactone ring by the alcohol, was demonstrated by the isolation of the isopropyl ester **24** when **12** was treated with isopropyl alcohol. The reactions of **2** and **12** with benzylamine in the absence of Lewis acid catalysis paralleled those with alcohols. Thus, **2** gave aziridine-2-carboxamide **25**, the product of lactone ring opening and N-deacetylation while the N-Cbz aziridine **12** yielded only the product of lactone ring opening, benzylamide **27**. As predicted by perturbational and HSAB (hard and soft acids and bases) theories, the regioselectivity of attack of **2** and **12** by soft nucleophiles is directed toward the center having the highest LUMO coefficient (C-2) (determined using MNDO calculations) while hard nucleophiles react with centers having the highest charge (C-1, C-1′). The synthetic potential of 2,3-aziridino γ-lactones of types **2** and **12**, as compared to the classical aziridine-2-carboxylic esters, is discussed in terms of these results.

Introduction

Aziridine-2-carboxylic esters **1** (Figure 1) are finding an ever-growing usefulness for the preparation of unnatural α- and β-amino acids,[1,2] and can serve as building blocks for the synthesis of biologically active molecules, for example actinomycin antibiotics,[3] mitomycin-related antitumor agents,[4] and kainic acid.[5] Medicinally and biologically important compounds are very often optically active. Access to optically pure aziridines **1** is thus of paramount importance, since it is the chirality at C-2 (**1**, R^3 = H) or at both C-2 and C-3 (**1**, $R^3 \neq$ H) which will be transferred to the final product, assuming a strictly S_N2-type opening of the aziridine ring at either of these centers.

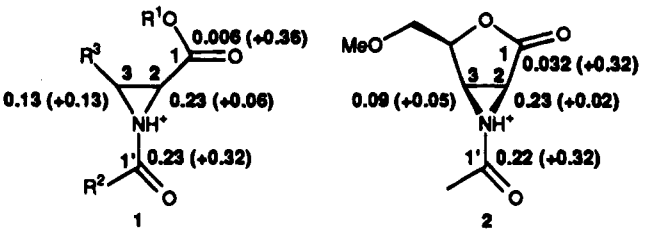

Figure 1. General structure of *N*-acylaziridine-2-carboxylic esters **1** and the structure of *N*-acetyl-2,3-aziridine γ-lactone **2** (protonated forms) used in this study. For **1** ($R_1 = R_2 = CH_3$; R_3 = H) and **2**, numbers outside parentheses are the LUMO coefficients while numbers inside parentheses correspond to charge distributions, both determined for C-1, C-2, C-3, and C-1′ using MNDO calculations (see ref 33 for details).

Although physical resolution of diastereomeric mixtures of aziridines **1** is possible,[6–8] the enantiomerically pure forms can be prepared using L-serine (R^3 = H)[6,9,10] or L-threonine ($R^3 = CH_3$)[4,10,11] as the primary source of

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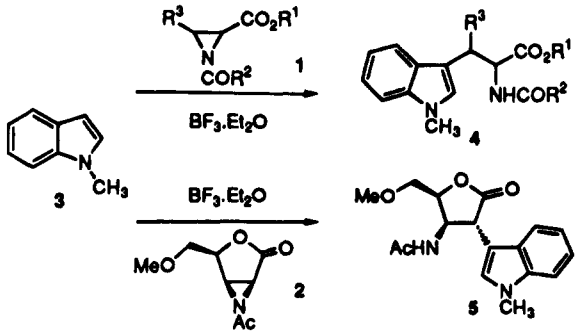
chirality. High optical yields of aziridines **1** have also been obtained by transformation of optically active oxiranes, the latter being obtained either by Sharpless epoxidation of allylic alcohols[12] or from D- or L-tartaric acid.[13,14] The use of oxiranes also allows a greater variety of R^3 groups to be incorporated on **1**, compared to the amino acid route. Garner and co-workers[15] have recently described the asymmetric synthesis of aziridines of type **1** (R^3 = H) by making use of Oppolzer's camphor-derived sultam as chiral auxiliary. This method was unsuccessful for the control of stereochemistry at C-3 (i.e., for R^3 = CH_3). The stereoselective preparation of 3-substituted aziridine-2-carboxylic esters can be achieved, however, by condensation of ester enolates of α-haloacetates with an imine having a dioxolane-type chiral auxiliary.[16] Evans[17] has shown that high enantiomeric excesses of 3-arylaziridine-2-carboxylic esters can be obtained by asymmetric aziridination of cinnamate esters with [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane in the presence of soluble chiral copper complexes.

In addition to their complete stereodefinition, the effective use of aziridine-2-carboxylic ester derivatives **1** as chirons in organic synthesis requires total regiocontrol of nucleophilic aziridine ring opening. Regioselective attack of **1** (R^3 = H, aryl, or alkyl group) at C-3 appears to be the rule for such nucleophiles as amines,[18] alcohols,[19-21] carboxylic acids,[1,22] thiols,[1,7,21-23] and indoles.[22,24-26] On the other hand, mixtures of products arising from both C-3 and C-2 attack (with the former generally predominating) have been obtained when Wittig[27] and organometallic reagents,[28] chloride (from hydrogen chloride),[1,22] azide (from sodium azide)[1] and malonates[29] were used as nucleophiles. Only a few examples of exclusive regioselectivity of attack at C-2 of

Scheme 1



1 by nucleophiles (e.g., azide from azidotrimethylsilane;[1] lithium dimethyl cuprate[2]) have been reported.

We have recently described the synthesis of 2,3-aziridino-2,3-dideoxy-D-lyxono-γ-lactones[30] of type **2** starting from D-ribose.[31] This represents a more flexible and preparatively useful synthesis than that described by Dreiding[32] (based on photogeneration of a nitrene species which reacts intramolecularly with a double bond), the only other known report concerning this type of compound. Lactones of type **2** may be seen as cyclic, rigid analogues of aziridine-2-carboxylic esters **1**. They presented several advantages to us compared to the classical esters **1**. Firstly, utilization of the carbohydrate chiral pool as starting point for the synthesis of **2** would allow optically pure and stereochemically defined C-3 substituted aziridines to be prepared. L- and D-α-amino acids would also become equally accessible, depending on whether the lyxo derivative **2** or its ribo analogue (synthesized from D-lyxose),[31] respectively, are the starting materials. Secondly, it could be expected that the extra strain present in **2** as a result of its fused bicyclic nature would enhance the reactivity of the aziridine ring toward nucleophilic ring opening. Thirdly, hydrolytic cleavage of the lactone ring after aziridine ring opening liberates another chirally pure center, the C-4 hydroxy group, amenable to further transformations.

It was with these considerations in mind and with the intention of forming β-substituted tryptophan derivatives, that **2** was reacted with 1-methylindole (**3**) in the presence of a Lewis acid.[33] However, whereas indole is known to react with aziridine-2-carboxylic esters **1** under these conditions exclusively at C-3 to give tryptophans **4**,[22,24-26] indole **3** was unexpectedly found to effect nucleophilic ring opening at position C-2 of lactone **2**, yielding **5** as the only isolable product (Scheme 1). In an attempt to rationalize this disparity in the reactivity pattern of **1** and **2**, use was made of perturbational and HSAB (hard and soft acids and bases) theories.[34,35] Thus,

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(30) A number of different nomenclatures are currently utilized to designate 5-membered lactones (e.g., γ-butyrolactones, furanones, butanolides). The IUPAC conventions recommend that lactones such as **2** containing a fused aziridine component be named as 3-oxa-6-azabicyclo[3.1.0]hexan-2-ones. This terminology, though cumbersome, has been used in the Experimental Section. However, in order to facilitate comparisons of the reactivity of lactones **2** and **12** with those of aziridine-2-carboxylic esters **1**, and also to emphasize their carbohydrate origins, the former compounds are referred to as 2,3-aziridino-2,3-dideoxy-D-lyxono-γ-lactones in the text. See: Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1984**, *44*, 2169.
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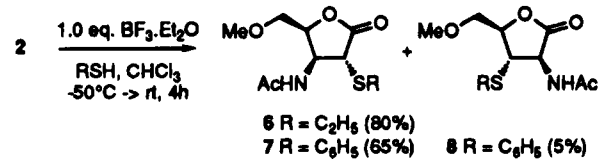
Scheme 2



application of semiempirical quantum mechanical MNDO calculations allowed the LUMO coefficients and charge distributions at C-1, C-2, C-3, and C-1′ of the protonated forms of both **1** and **2** to be determined[33] (Figure 1). Results showed that, in the case of a soft nucleophile such as 1-methylindole (**3**), whose reactivity with an electrophile is under orbital control, attack at C-2 of lactone **2** was theoretically favored over attack at C-3 since the LUMO coefficient at the former position (0.23) is substantially larger than that at the latter (0.09). This, of course, is borne out experimentally by the formation of **5**.[36]

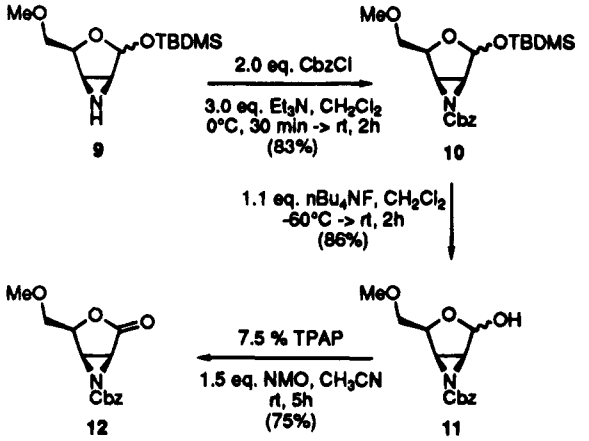
In order to test the validity of MNDO calculations in predicting the reactivity pattern of aziridine-γ-lactones, we have subjected the latter to reaction with a variety of nucleophiles. These nucleophiles were chosen as a function of their relative hardness or softness and, for the sake of comparison, of their documented reactivity with aziridine-2-carboxylic esters **1**. The results reported herein indicate that MNDO calculations can effectively predict the regioselectivity of nucleophilic attack of 2,3-aziridino-2,3-dideoxy-D-lyxono-γ-lactones. This, together with the latter's substantially different reactivity profile compared to **1**, makes these compounds potentially valuable chiral synthons.

Results and Discussion

It was first decided to study the ring opening of aziridine **2** using soft, thiol-type nucleophiles. While boron trifluoride etherate-catalyzed ring opening of aziridine-2-carboxylic esters **1** (with or without a substituent at C-3) with thiols has been shown to always occur at C-3,[1,7,21-23] treatment of **2** with excess ethanethiol under the same conditions gave, in 80% yield, compound **6** only, the product of C-2 attack (Scheme 2). The xylo configuration of **6** was indicated by its ^{1}H NMR spectrum, the pattern of ring proton resonances being very similar to that of compound **5**, whose structure has been proven unambiguously by NOESY experiments.[33] In particular, the appearance of H-2 as a simple doublet in compound **6**, as well as in all the products of C-2 attack to be described, is characteristic.[1,32] Furthermore, a *trans* relationship between H-2 and H-3, indicative of S_N2 attack of the aziridine ring, as always observed for C-3 alkyl substituted aziridine-2-carboxylic esters,[1,13,23] was demonstrated by the relatively large coupling constant (7.5 Hz) between these two protons.[32,37]

When the reaction with **2** was repeated using thiophenol, the product of C-2 attack, compound **7**, was again the major product (65%). However, in contrast to the reaction with ethanethiol, a small amount (5%) of the C-3 substitution product, **8**, was also formed. Structural assignment of **8** was also based on the coupling characteristics of H-2 in the ^{1}H NMR spectrum. In this case, H-2 exists as a doublet of doublets due to coupling with both H-3 and the acetamide proton.[1,32]

Scheme 3



Compound **2** thus behaves toward thiol-type soft nucleophiles as predicted, showing predominant, or even exclusive, attack on the nucleophilic center having the highest LUMO coefficient (C-2). However, a notable difference between synthon **2** and the aziridine-2-carboxylic ester, used by others[21,23] for their systematic ring opening reactions with thiols, is the presence of a Cbz activating group on the aziridine nitrogen atom of the latter instead of an acetate group (our case). Because the nature of the electron-withdrawing group of the aziridine nitrogen atom has been shown to affect the reactivity of these systems[1] and in order to see if the regioselectivity of ring opening of **2** by thiols is affected by the N-protecting group, the N-Cbz analogue of **2**, that is compound **12**, was synthesized as shown in Scheme 3 using a methodology previously described by us.[31] Thus, the *tert*-butyldimethylsilyl 2,3-aziridinolyxofuranoside (**9**) was first treated with benzyl chloroformate in the presence of triethylamine giving the N-Cbz aziridine derivative **10**. Cleavage of the silyl blocking group with tetrabutylammonium fluoride followed by oxidation of the resulting free anomeric hydroxyl group of **11** using tetrapropylammonium perruthenate (TPAP) furnished the desired lactone **12**, whose spectral characteristics were in full accord with the assigned structure.

The charge distributions and LUMO coefficients at C-1, C-2, C-3, and C-1′ of **12** in both its ground state and protonated state were determined using MNDO calculations as previously described for compound **2**.[33] Results are given in Figure 2 for the most stable (i.e. lowest energy) structures in each case. The latter are depicted in Figure 3.

As is evident from Figure 2, the LUMO coefficient at C-2 of **12** (0.20) is again superior to that at C-3 (0.14), as in the case of the N-acetylated γ-lactone **2**. It thus came as no surprise that **12** reacted with ethanethiol in the presence of boron trifluoride etherate to give exclusively the product of C-2 attack, compound **13** (Scheme 4), confirming that this regioselectivity, as opposed to C-3 regioselectivity in the aziridine–ester series, is more a particularity of the lactone structure than of the nature of the group on the aziridine nitrogen atom.[38]

(36) The LUMO coefficients at C-2 (0.23) and C-3 (0.13) of the aziridine ester **1** ($R^1 = R^2 = CH_3$; $R^3 = H$) being essentially the same as those of the equivalent atoms of lactone **2**, the formation of compound **4** (from **1** and **3**) is, in orbital terms, paradoxical. We have previously suggested[33] that the reason for this may be that steric factors (due to the flexible ester side chain at C-2 of **1**) apparently override orbital factors in this case so that nucleophilic attack at the sterically less hindered C-3 position is favored.

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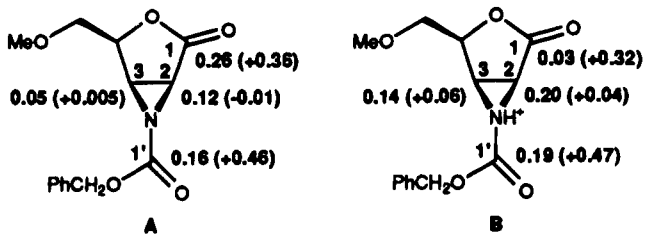


Figure 2. Calculated LUMO coefficients and (in parentheses) charge distributions for compound **12** in the ground state (A, LUMO energy = 0.38 eV) and in the N-protonated state (B, LUMO energy = −5.27 eV).

The N-Cbz aziridine **12** similarly reacted with other soft nucleophiles in the presence of boron trifluoride etherate to give exclusively products of C-2 attack. Thus, acetic acid, a nucleophile known to open aziridine-2-carboxylic esters at C-3,[1,22] provided a 57% yield of the 2-acetoxy-3-aminoxylonolactone derivative **14** while lithium bromide gave a high yield of the novel 2-bromo-3-aminoxylonolactone derivative **15**. Structural elucidation of **15** was aided by the very close resemblance between its ^{1}H NMR spectrum and the reported NMR data for its 3-*O*-acetyl analogue, particularly with regard to H-2 and H-3 resonances and coupling constants.[37] Although the reaction of aziridine-2-carboxylic esters **1** with lithium bromide has not been reported, their reaction with hydrogen chloride in ether[1] yields the 3-chloro α-amino acid when the aziridine nitrogen is activated with an acetate group. However, when tosyl is the activating group, 2-chloro β-amino acid formation predominates.

We next investigated the behavior of aziridine γ-lactones **2** and **12** toward hard nucleophiles, in particular toward methanol and benzyl alcohol. Theory predicts that the regioselectivity of attack of such nucleophiles is under charge control rather than orbital control. These alcohols should thus preferentially react with centers having the highest positive charge distribution. For aziridines **2** and **12** in the protonated state, MNDO calculations have shown these centers to be, in decreasing order of charge and, thus, of reactivity: C-1′ ≥ C-1 ≫ C-3 > C-2 (Figures 1 and 2). This charge distribution is essentially the same as that calculated for the corresponding centers of the aziridine-2-carboxylic ester **1** ($R^1 = R^2 = CH_3$; $R^3 = H$). Of C-2 and C-3, the latter would be predicted to be attacked preferentially by hard nucleophiles. Aziridine-2-carboxylic esters of type **1** ($R^2 = OCH_2Ph$; $R^3 = H$ or CH_3) have, in fact, been opened with a variety of alcohols, including methanol and benzyl alcohol, in the presence of boron trifluoride etherate, regioselective aziridine ring opening at C-3 being observed in all cases.[19,21] Vessiere and co-workers[20] have reported this same regioselectivity under identical reaction conditions using *N*-alkylaziridine-2-carboxylic esters.

The reaction of **2** with alcohols proved to be somewhat more complex, however. Thus, treatment of **2** with excess benzyl alcohol in chloroform under the usual conditions (i.e., procedure A, 2 equiv of boron trifluoride etherate followed by aqueous sodium hydrogen carbonate workup) gave, after chromatography on silica gel, the deacetylated benzyl aziridine-2-carboxylate **17** (35% yield) and the benzyl 2-acetamido-3-(benzyloxy)pentanoate derivative **18** (30%) (Scheme 5). The latter was always obtained contaminated with lactone **19**, presumably formed by cyclization of **18** on the chromatography column since **19** could not be detected by ^{1}H NMR in the crude reaction mixture (**17** + **18**) i.e., before chromatography.[39] A modification of the workup procedure in this reaction allowed complete *in situ* transformation of **18** into **19**. Thus, after treatment of **2** with benzyl alcohol and 2 equiv of boron trifluoride etherate in chloroform as before, the reaction mixture was concentrated *in vacuo* at 30−50 °C at the end of the reaction period (procedure B) before being neutralized with sodium hydrogen carbonate. This furnished compounds **17** and **19** (30% and 35%, respectively) with no trace of uncyclized compound **18**.

Both the regio- and diastereoselectivity of the reaction of benzyl alcohol with **2** were also evident from the ^{1}H NMR spectra of **18** and **19**. Thus, H-2 was observed in both compounds as a doublet of doublets, in contrast to the products of C-2 attack (e.g., **6**, **7**, **13**−**15**) in which H-2 systematically appears as a doublet. The H-2, H-3 coupling constant of 5.6 Hz in **19** is in the range expected for a *trans* relationship thereby pointing to an *anti* geometry for these protons in the precursor **18**, the result, in turn, of S_N2 opening of the aziridine ring of **16**.

Perturbational theory predicts the formation of compound **17** from **2** and a hard nucleophile such as benzyl alcohol. The reactivity of these two entities is now under charge control (rather than under orbital control as in the case of the soft nucleophiles described above) and the sites of highest charge on **2** in its protonated form are the carbon atoms of the lactone and acetyl carbonyls (C-1 and C-1′ respectively), calculated to be +0.32 for both atoms (Figure 1). In comparison, the charges at C-2 and C-3 are only +0.02 and +0.05, respectively. Although the apparent equivalence of the charges on C-1 and C-1′ of protonated **2** would suggest that these two centers should react simultaneously with benzyl alcohol (to give exclusively **17**), the relief of ring strain that occurs when the lactone ring is opened may favor this process over that of N-deacetylation. This would also explain why transesterifications of aziridine-2-carboxylic esters (e.g. methyl esters) apparently do not occur when these are treated with various alcohols in the presence of a Lewis acid.[19−21] Access to the acetamido carbonyl group is also

(38) Although **12** was not reacted with thiophenol as was **2** (Scheme 2), we have recently observed that the 5-methoxycarbonyl analogues of **2** and **12** react with this nucleophile to also give exclusively the products of C-2 attack, further substantiating the relative innocuity of the *N*-acyl group in controlling the general regioselective course of the reactions in this family of aziridines. These results will be reported in due course.

(39) The formation of **17** and **18** is probably best explained by an initial attack of benzyl alcohol at the lactone carbonyl of **2** to give the benzyl *N*-acetylaziridine-2-carboxylate derivative **16** as intermediate. Further attack of **16** by the nucleophile yields the deacetylated aziridine **17** which, now deactivated, can no longer undergo further ring opening. Moreover, **17** is prevented from recycling to the γ-lactone form due to the rigidity provided by the aziridine ring. Alternatively, benzyl alcohol may react with intermediate **16** (now an aziridine-2-carboxylic ester of type **1**) at the expected C-3 position to give ring-opened product **18** which, in contrast to **17**, is free to cyclize to lactone **19** under the mild acidic conditions provided by chromatography on silica gel. The structure of **17** was confirmed by infrared and ^{1}H NMR spectroscopy. This compound displayed a prominent hydroxyl band in the IR as well as a single ester (rather than lactone) carbonyl absorption at 1740 cm^{-1}. The incorporation of a benzyl moiety and the absence of an acetamido group was also obvious from the ^{1}H NMR spectrum of **17**. On the other hand, compound **18** showed, in addition to an OH band, absorptions due to two distinct carbonyl groups (ester and amide) in the IR while its ^{1}H NMR spectrum indicated the presence of two benzyloxy moieties, one an ether, the other an ester, as well as an acetamido group. The cyclized form of **18**, that is **19**, showed the expected lactone absorption at 1788 cm^{-1} in the IR and its ^{1}H NMR spectrum now displayed a single benzyloxy group. The mass spectral data for compounds **17**−**19** were alsc in full accord with these assigned structures.

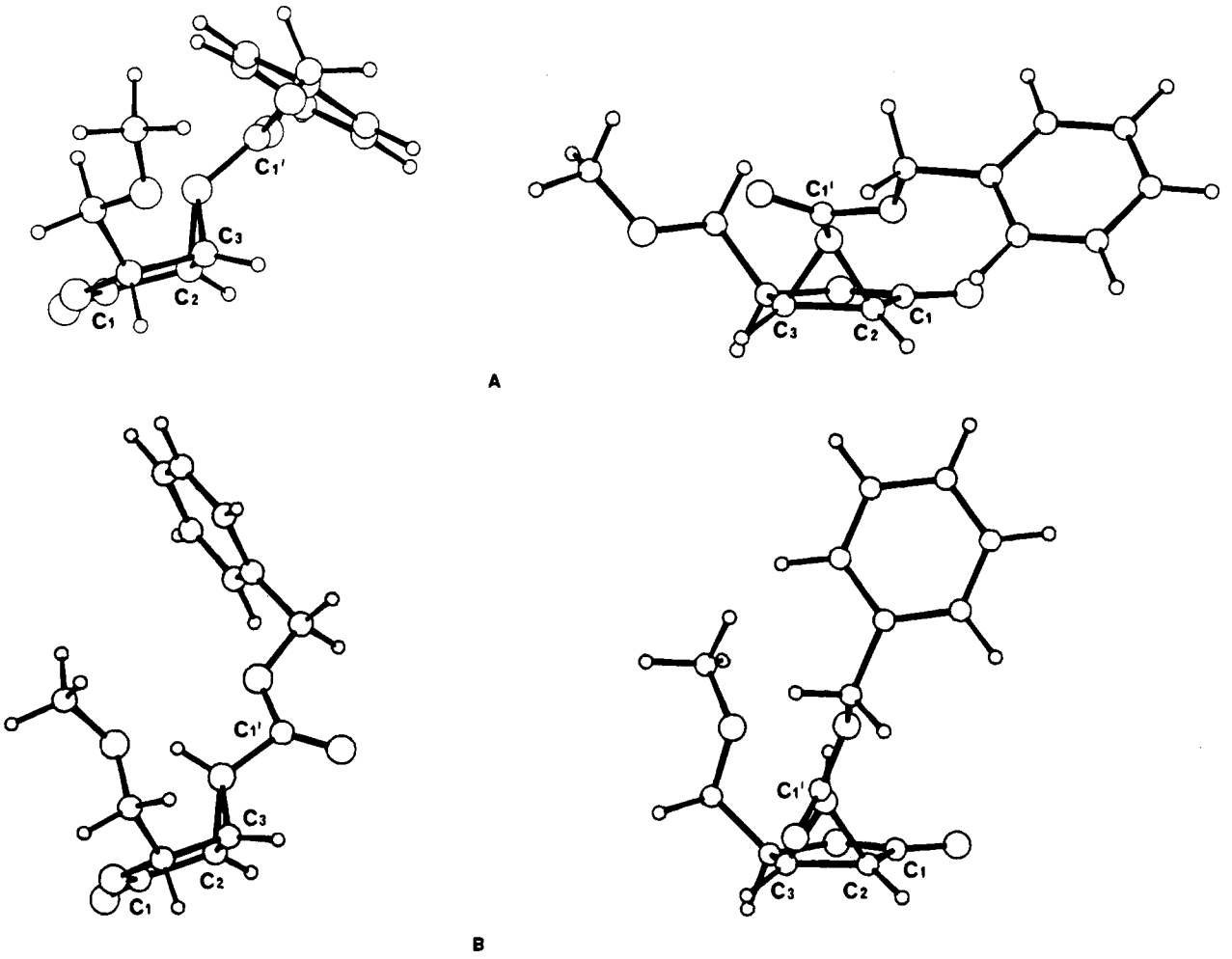
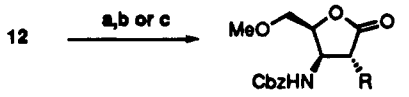


Figure 3. Two views of the minimized structures of compound **12** in the ground state (A) and in the N-protonated state (B). Minimizations were performed using MOPAC.

Scheme 4



13 R = SC_2H_5
14 R = OAc
15 R = Br

a- 1.0 eq. $BF_3.Et_2O$, C_2H_5SH, $CHCl_3$, -50°C -> rt, 4h (13 : 76%)
b- 1.0 eq. $BF_3.Et_2O$, AcOH, $CHCl_3$, 60°C, 1h30 (14 : 57%)
c- 2.0 eq. $BF_3.Et_2O$, 4.0 eq. LiBr, $CHCl_3$, -20°C -> rt, 4h (15 : 80%)

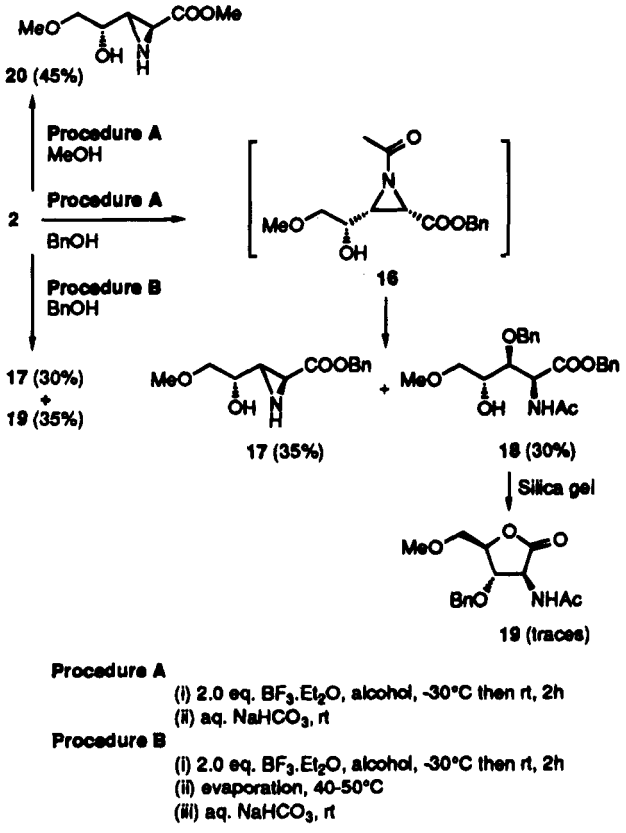
hindered by the presence of the bulky Lewis acid (BF_3–Et_2O), not taken into account in our MNDO calculations, where Lewis acid complexation at this site was simulated by protonation, simpler to compute.[33,40,41] The reality of this hindrance is demonstrated by the observation that treatment of **2** with methanol, a substantially smaller nucleophile than benzyl alcohol, affords almost exclusively the deacetylated product **20** (i.e., the methyl ester analogue of **17**) with only traces of N-acetylated compound analogous to **18** (which was not characterized).

As observed here, and as noted by others,[1] C-3 alkyl (as opposed to C-3 aryl) aziridine-2-carboxylic esters that are not substituted by an electron-withdrawing group on the aziridine nitrogen (as in compound **17**) are resistant to nucleophilic ring opening even in the presence of Lewis acids. Chirons of type **2** would thus be more synthetically useful if only a single reaction product (i.e. analogous to **18** or **19**) were obtained upon treatment with a hard nucleophile. This could be best achieved by ensuring that N-deacylation (and thus, deactivation) does not occur during the course of the reaction. It was hoped that, despite the large relative charge on the carbonyl of the Cbz group of **12** (+0.47) as compared to that on the acetamide carbonyl on **2** (+0.32), the large steric hindrance provided by the benzyl carbamate would inhibit the formation of compounds of type **17** and **20** and favor, as a consequence, aziridine ring opening. This in fact proved to be the case when the *N*-(benzyloxycarbonyl)-aziridine **12** was treated with methanol or benzyl alcohol via procedure B, giving 3-alkoxy-2-(benzyloxycarbonyl)-

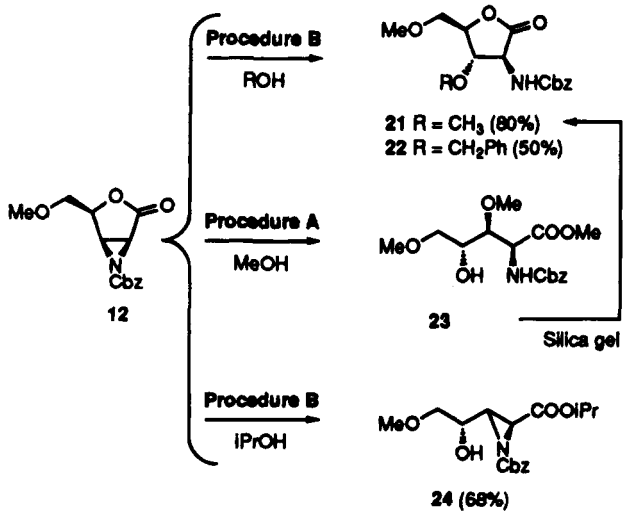
(40) Nishiguchi, T.; Tochio, H.; Nabeya, A.; Iwakura, Y. *J. Am. Chem. Soc.* **1969**, *91*, 5841.

(41) We have been able to study the effect which complexation with BH_3, a bulkier acid than H^+, has on the LUMO coefficients and charge distribution of **12** using MOPAC.[42,43] For the most stable conformation of **12**, the LUMO coefficients were calculated to be 0.15 and 0.09 for C-2 and C-3, respectively, while the charges were +0.01 and +0.04 for these same atoms. At C-1 and C-1′, the charges were determined to be +0.33 and +0.47, respectively. These values are thus practically identical to those found for the N-protonated form of **12** (Figure 2), suggesting that simulation of BF_3 complexation by H^+ complexation is a valid simplification as far as MNDO calculations are concerned. It must nevertheless be kept in mind that this simplification does not present a true picture of the steric environment in the vicinity of the site of complexation, that is, the *N*-acyl function.

Scheme 5



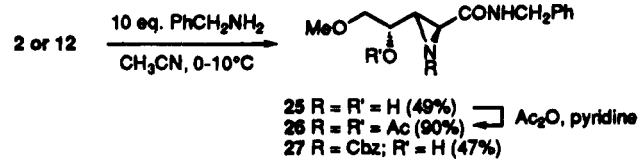
Scheme 6



amino-γ-lactone derivatives **21** and **22**, respectively, as sole isolable products (Scheme 6). The intermediacy of a β-hydroxy ester (analogous to **18**) in the formation of these lactones was again demonstrated by the identification of compound **23** as the major product (before chromatography) when aziridine **12** was treated with methanol via procedure A. As with **18**, purification of **23** on silica gel led to lactonization, affording compound **21**.

An interesting result was obtained when **12** was treated with isopropyl alcohol using procedure B. In this case, only the product of lactone opening, that is, isopropyl ester **24**, was formed, the bulkiness of the isopropyl group presumably being responsible for its failure to effect subsequent aziridine ring opening. The isolation of **24** is important in that it substantiates the intermediacy of the hypothesized precursor **16** (Scheme 5) and

Scheme 7



provides proof that lactone ring opening is the first step in the reaction of **2** and **12** with hard nucleophiles as typified by alcohols.

Finally, the reactivity of lactones **2** and **12** toward benzylamine, also a hard nucleophile, was examined. The reactions were performed in acetonitrile in the absence of acidic catalyst since the latter would tend to prefer complexation with the nucleophile rather than with the less basic aziridine carboxamide. Under these conditions, the N-acetylated aziridine **2** behaved toward benzylamine in much the same way as it did toward benzyl alcohol, that is, by N-deacetylation and lactone ring opening to give the aziridine-2-carboxamide **25** (Scheme 7) (characterized as its diacetate **26** after treatment with acetic anhydride in pyridine). However, in contrast to the reaction of **2** with benzyl alcohol, deacetylation of **2** was complete, eliminating the possibility of opening the now deactivated aziridine ring to give a compound analogous to **18**. The fact that, in this case, the N-acetyl carbonyl group is not hindered by boron trifluoride etherate complexation, can explain this difference in product distribution in the two reactions. The observed reactivity of lactone **2** toward benzylamine is, furthermore, that predicted from MNDO calculations since, even in the unprotonated state, the highest charge distributions have been shown to be localized on the two carbonyl carbons, C-1 and C-1′ (+0.37 and +0.32, respectively), charges at C-2 and C-3 (−0.03 and +0.005, respectively) being negligible.[33] Although the reaction of *N*-acylaziridine-2-carboxylates with amines has not been reported, Okawa and co-workers[18] have described such reactions using aziridine-2-carboxamide analogues also in the absence of acid catalysis. No product arising from opening of the aziridine ring by benzylamine was observed by these authors, a result consistent with both our results and our calculations.

Analogously, reaction of benzylamine with the *N*-(benzyloxycarbonyl)aziridine **12** under the same conditions as with **2** afforded a single product, **27**, resulting from attack of the lactone carbonyl, that is, the site having in the ground state the highest charge (+0.36) after the Cbz carbonyl (+0.46) (Figure 2). The latter, in contrast to the acetamide group of **2** and for the same reasons of steric impedement invoked above with respect to formation of compounds **21**−**24**, was left intact by this treatment.

Summary and Conclusions

Our initial observation that, in the presence of a Lewis acid, 2,3-aziridino-2,3-dideoxy-D-lyxono-γ-lactone (i.e., **2**) is unexpectedly attacked by *N*-methylindole (**3**) exclusively at position C-2 (to give **5**), in contrast to aziridine-2-carboxylic esters (**1**) which are invariably attacked by this nucleophile at C-3 (to give **4**), prompted us to attempt to rationalize the dichotomous behavior of these chemically related systems using perturbation theory and MNDO calculations.[33] The latter was in fact successful in explaining the reactivity of **2** toward indole and,

moreover, predicted that soft nucleophiles in general should behave similarly. The present study demonstrates that this prediction is correct. Thus, besides the previously reported *N*-methylindole[33] and azide,[32] soft nucleophiles represented by thiols, acetate, and halide, known to attack aziridine-2-carboxylic esters **1** at C-3, effect aziridine ring opening of lactone **2** and its Cbz analogue **12** preferentially and, in practically all cases, exclusively at C-2. In the case of hard nucleophiles such as alcohols, although the overall result is regioselective opening of the aziridine ring of **2** and **12** at C-3 (e.g. compounds **19**, **21**, **22**), these compounds were shown to be the result of nucleophilic attack of an aziridine-2-carboxylic ester intermediate (e.g. **16**), itself the result of initial lactone ring opening by the alcohol. These observations were also satisfyingly accounted for by MNDO calculations, as were the products of the reactions of **2** and **12** with benzylamine under nonacidic conditions, wherein lactone ring opening is also the main reaction pathway.

From a synthetic point of view, 2,3-aziridino γ-lactones should prove to be valuable chirons for the preparation of more complex, optically active substances. In addition to the complete diastereoselectivity of aziridine ring opening in these systems, giving rise to two stereodefined centers, the regioselectivity of nucleophilic attack, whether at C-1, C-2, C-3, or C-1′, can also be controlled, as this study demonstrates. In particular, the propensity of soft nucleophiles to attack exclusively the C-2 position of the 2,3-aziridino γ-lactones allows access to β-amino acids which would generally be unavailable starting from aziridine-2-carboxylic esters **1**, prone to C-3 attack by most nucleophiles and thus, to generation of α-amino acids.

Finally, the lactone ring of chirons **2** and **12** masks a third stereochemically pure center, the C-4 hydroxyl group (e.g., compounds **23**–**27**) which can, moreover, serve as a functional group for further transformations. In fact, compound **24** represents one of the few known examples of an aziridine-2-carboxylic ester bearing a chiral, functionalized C-3 substituent.[4,32] The application of these two properties of molecules of type **2** and **12** (i.e. C-2 regioselectivity and a complex C-3 substituent) to the synthesis of biologically important molecules is in progress.

Computational Methods

The methodology used to calculate the LUMO coefficients and charge distributions at C-1, C-2, C-3, and C-1′ of compound **12** in its ground state and in its protonated state was essentially identical to that previously described by us[33] for similar calculations on **2**. Briefly, geometry optimizations were carried out at the MNDO restricted Hartree–Fock (RHF) level using the MOPAC program (version 5.0).[42] Though boron trifluoride etherate was used in the experiments, MOPAC calculations were simplified by simulating the approach of a proton toward the aziridine ring nitrogen atom.[40] Only N-protonation (rather than O-protonation) of the amide bond was taken into account for reasons previously discussed.[33] The lowest energy conformations of **12** were first determined by considering two degrees of freedom: the dihedral angle formed by C-2, N, C-1′, =O and that formed by C-3, C-4, C-5, O. The enthalpies of formation of the ground state and protonated products were determined as a function of these dihedral angles and with the nitrogen lone pair (or its associated proton in the case of the protonated species) either in a *syn* or an *anti* position with respect to the plane of the γ-lactone ring. After the minimum energy conformations were obtained, the rotational barriers presented by the flexible benzyloxy chain were then computed. Finally, full geometry optimizations were performed and the LUMO coefficients and charge distributions of the minimized structures were calculated. Results are given in Figures 2 and 3. The Z matrices for all computed structures are available from the authors.

(42) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.
(43) Dewar, M. J. S.; McKee, M. L. *J. Am. Chem. Soc.* **1977**, *99*, 5231.

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). ^1H 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. Element analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

***tert*-Butyldimethylsilyl *N*-(Benzyloxycarbonyl)-2,3-aziridino-2,3-dideoxy-5-*O*-methyl-α-(and β)-D-lyxofuranoside (10).** To a solution of aziridine **9** (950 mg, 3.66 mmol) and triethylamine (1.55 mL, 10 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise under nitrogen benzyl chloroformate (1.05 mL, 7.3 mmol). The reaction mixture was stirred at 0 °C for 30 min and then for 2 h at rt. The mixture was diluted with CH_2Cl_2 (25 mL) and washed with water (2 × 20 mL). The organic phase was dried over Na_2SO_4, the solvents were removed *in vacuo*, and the residue was purified by column chromatography on silica gel using heptane–ethyl acetate (4:1 followed by 3:1) as eluent. The minor α anomer of **10** eluted first (150 mg, 10%): ^1H NMR (250 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 3.22 (d, 1H, J = 4.5 Hz), 3.36 (dd, 1H, J = 4.5, 1.1 Hz), 3.39 (s, 3H), 3.63 (d, 2H, J = 5.9 Hz), 4.22 (dt, J = 1.1, 5.9 Hz), 5.13 (2d, 2H), 5.39 (s, 1H), 7.35 (s, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −4.4, −4.1, 17.8, 25.7, 41.7, 44.8, 59.3, 68.2, 71.4, 75.3, 96.2, 128.2, 128.4, 128.6, 135.8, 161.0; mass spectrum (CI) *m/z* 394 $(MH)^+$.

Continued elution of the column gave the major β anomer of **10** (1.05 g, 73%), obtained as a colorless oil: $[\alpha]^{23}_D$ −16.4° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.90 (s, 9H), 3.29 (m, 2H), 3.40 (s, 3H), 3.65 (ddd, 2H, J = 6.1 Hz), 3.93 (dt, 1H, J = 6.1, 1.3 Hz), 5.13 (s, 2H), 5.36 (d, 1H, J = 1.0 Hz), 7.34 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.8, 18.0, 25.8, 42.6, 44.6, 59.4, 68.3, 71.9, 75.3, 96.9, 127.9, 128.3, 128.5, 135.7, 161.8; IR (film) 1728 cm^{-1}; mass spectrum (CI) *m/z* 394 $(MH)^+$. Anal. Calcd for $C_{20}H_{31}NO_5Si$: C, 61.03; H, 7.94; N, 3.56. Found: C, 60.63; H, 7.87; N, 3.29.

***N*-(Benzyloxycarbonyl)-2,3-aziridino-2,3-dideoxy-5-*O*-methyl-α,β-D-lyxofuranose (11).** A solution of compound **10** (1.25 g, 3.17 mmol) in CH_2Cl_2 (18 mL) was treated at −60 °C under nitrogen with TBAF trihydrate (1.10 g, 3.5 mmol). The reaction mixture was allowed to slowly rise to rt. After 2 h, the solution was concentrated under vacuum and the crude product was filtered through a pad of silica gel (ethyl acetate–heptane 3:2) giving compound **11** as a white solid (760 mg, 86%): mp 70–73 °C; $[\alpha]^{23}_D$ +4.3° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.32 (d, 1H, J = 4.4 Hz), 3.35 (dd, 1H, J = 4.4, 1.4 Hz), 3.39 (s, 3H), 3.60 (dd, 1H, J = 7.1, 10.0 Hz), 3.66 (dd,

1H, J = 5.1, 10.0 Hz), 4.20 (br m, 1H, exchangeable with D_2O), 4.34 (ddd, 1H, J = 1.4, 6.6, 5.5 Hz), 5.13 (s, 2H), 5.47 (d, 1H, J = 1.5 Hz), 7.35 (s, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.2, 43.7, 59.3, 68.5, 71.5, 75.1, 95.7, 128.2, 128.5, 128.6, 135.4, 161.2; IR (film) 3362, 1729 cm^{-1}; mass spectrum (HRCI) calcd for $C_{14}H_{18}NO_5$ m/z 280.1185 $(MH)^+$; found 280.1190.

(1*S*,4*S*,5*R*)-*N*-(Benzyloxycarbonyl)-4-(methoxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (12). A solution of compound **11** (350 mg, 1.25 mmol) in acetonitrile (10 mL) was stirred for 5 h at rt under nitrogen in the presence of TPAP (33 mg, 0.09 mmol), 4-methylmorpholine *N*-oxide (220 mg, 1.9 mmol), and powdered 4 Å molecular sieves (625 mg). The mixture was then concentrated *in vacuo*, the residue was taken up in ethyl acetate, and the resulting suspension was filtered through a pad of silica gel. Compound **12**, obtained in 75% yield (275 mg) as a white solid after evaporation of the filtrate, could be used in the following steps without further purification. An analytical sample was obtained by chromatography of this material on a column of silica gel using ethyl acetate–heptane (1:1) as eluent:mp 113.5–114 °C; $[\alpha]^{22}_D$ −32.9° (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.41 (s, 3H), 3.59 (d, 1H, J = 4.3 Hz), 3.67 (dd, 1H, J = 6.4, 10.0 Hz), 3.74 (dd, 1H, J = 6.1, 10.0 Hz), 3.76 (dd, 1H, J = 2.7, 4.3 Hz), 4.62 (dt, 1H, J = 2.7, 6.1 Hz), 5.17 (s, 2H), 7.37 (s, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 38.1, 41.7, 59.6, 69.3, 70.5, 77.4, 128.4, 128.7, 128.8, 134.8, 159.6, 168.6; IR (film) 1733, 1793 cm^{-1}; mass spectrum (CI) m/z 278 $(MH)^+$, 234 $(MH - CO_2)^+$. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.49; H, 5.51; N, 5.05.

General Procedure for the Opening of 2 and 12 by Thiols. To a solution of **2** or **12** (0.25 mmol) in $CHCl_3$ (1.5 mL) and thiol (ethanethiol or thiophenol) (1.5 mL) was added at −50 °C under nitrogen boron trifluoride etherate (30 μL, 0.25 mmol). The reaction mixture was then allowed to come to rt and was stirred for 4 h before saturated aqueous $NaHCO_3$ (5 mL) was added. The mixture was extracted with ethyl acetate (2 × 10 mL), the combined organic phases were dried over Na_2SO_4, and the solvents were removed under vacuum. The crude reaction products (**6**, **7**, **8**, **13**) were purified by flash chromatography on silica gel using the solvent systems indicated below.

3-Acetamido-2,3-dideoxy-2-(ethylthio)-5-*O*-methyl-D-xylono-1,4-lactone (6) was obtained from **2** and ethanethiol as an oil in 80% yield after chromatography using ethyl acetate as eluent: $[\alpha]^{22}_D$ +68.1° (*c* 2.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.3 Hz), 2.06 (s, 3H), 2.77 (q, 2H), 3.41 (s, 3H), 3.62 (d, 1H, J = 7.5 Hz), 3.71 (d, 2H, J = 2.0 Hz), 4.72 (dt, 1H, J = 7.5, 2.0 Hz), 4.80 (ddd, 1H), 6.52 (d, 1H, exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 23.3, 25.1, 47.1, 53.3, 59.9, 71.2, 78.0, 170.7, 173.5; IR (film) 1540, 1660, 1781, 3280 cm^{-1}; mass spectrum (EI) m/z 247 $(M)^+$, 188 $(M - AcNH_2)^+$. Anal. Calcd for $C_{10}H_{17}NO_4S$: C, 48.57; H, 6.93; N, 5.66; S, 12.96. Found: C, 48.86; H, 6.76; N, 5.50; S, 13.09.

3-Acetamido-2,3-dideoxy-5-*O*-methyl-2-(phenylthio)-D-xylono-1,4-lactone (7) and 2-Acetamido-2,3-dideoxy-5-*O*-methyl-3-(phenylthio)-D-arabinono-1,4-lactone (8). Both compounds were obtained from **2** and thiophenol. Elution of the chromatography column with ethyl acetate–heptane (2:1) first gave compound **8** (4 mg, 5%) as an oil: ^1H NMR (250 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.36 (s, 3H), 3.59 (dd, 1H, J = 3.9, 11.6 Hz), 3.72 (dd, 1H, J = 2.0, 11.6 Hz), 3.83 (dd, 1H, J = 10.7, 9.2 Hz), 4.32 (ddd, 1H, J = 9.2, 3.9, 2.0 Hz), 4.63 (dd, 1H, J = 10.7, 8.5 Hz), 6.01 (d, 1H, J = 8.5 Hz, exchangeable with D_2O), 7.37 (m, 3H), 7.54 (m, 2H); mass spectrum (EI) m/z 295 $(M)^+$, 236 $(M - AcNH_2)^+$.

Continued elution of the column with ethyl acetate–heptane (4:1) gave compound **7** (48 mg, 65%) as a white solid: mp 146 °C; $[\alpha]^{22}_D$ +93.5° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.38 (s, 3H), 3.64 (ddd, 2H, J = 11.5, 1.8, 1.5 Hz), 3.89 (d, 1H, J = 10.2 Hz), 4.51 (dt, 1H, J = 8.0, 1.5, 1.8 Hz), 4.87 (ddd, 1H, J = 10.2, 8.0 Hz), 6.13 (d, 1H, exchangeable with D_2O), 7.35 (m, 3H), 7.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 51.2, 51.9, 59.9, 71.4, 77.4, 129.3, 129.4, 131.6, 135.2, 170.4, 172.3; IR (film) 1540, 1665, 1782, 3290, 3360 cm^{-1}; mass spectrum (EI) m/z 295 $(M)^+$, 236 $(M - AcNH_2)^+$. Anal. Calcd for $C_{14}H_{17}NO_4S \cdot 0.1\ H_2O$: C, 56.60; H, 5.80; N, 4.70; S, 10.78. Found: C, 56.96; H, 5.89; N, 4.71; S, 10.38.

3-[*N*-(Benzyloxycarbonyl)amino]-2,3-dideoxy-2-(ethylthio)-5-*O*-methyl-D-xylono-1,4-lactone (13) was obtained from **12** and ethanethiol as an oil in 76% yield after chromatography using heptane–ethyl acetate (7:3) as eluent: $[\alpha]^{22}_D$ +62.8° (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.4 Hz), 2.76 (q, 2H, J = 7.4 Hz), 3.37 (s, 3H), 3.60 (d, 1H, J = 8.3 Hz), 3.66 (dd, 1H, J = 11.5, 1.6 Hz), 3.73 (dd, 1H, J = 11.5, 1.0 Hz), 4.60 (m, 1H), 4.64 (m, 1H), 5.14 (s, 2H), 5.55 (d, 1H, J = 7.4 Hz, exchangeable with D_2O), 7.37 (s, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.3, 25.1, 47.4, 55.1, 59.9, 67.6, 71.4, 77.7, 128.4, 128.6, 128.7, 158.0, 173.1; IR (film) 1712, 1781, 3325 cm^{-1}; mass spectrum (EI) m/z 339 $(M)^+$, 204 $(M - PhCH_2CO_2)^+$. Anal. Calcd for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13. Found: C, 56.59; H, 6.26; N, 4.16.

2-*O*-Acetyl-3-[*N*-(benzyloxycarbonyl)amino]-3-deoxy-5-*O*-methyl-D-xylono-1,4-lactone (14). To a solution of compound **12** (36 mg, 0.13 mmol) in $CHCl_3$ (1.5 mL) and acetic acid (1 mL) held at −30 °C under nitrogen was added boron trifluoride etherate (16 μL, 0.13 mmol). The reaction mixture was heated at 60 °C for 1.5 h, cooled, and saturated aqueous $NaHCO_3$ (5 mL) was added. The mixture was extracted with ethyl acetate (2 × 10 mL), the combined organic extracts were dried over Na_2SO_4 and the solvents were removed *in vacuo*. Chromatography of the crude product on silica gel (ethyl acetate–heptane 1:1) gave 25 mg (57%) of compound **14** as an oil: $[\alpha]^{22}_D$ +55.4° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.38 (s, 3H), 3.64 (ddd, 2H, J = 1.2, 1.0, 11.5 Hz), 4.76 (m, 1H), 4.79 (ddd, 1H, J = 6.7 Hz), 5.12 (s, 2H), 5.52 (d, 1H, J = 6.7 Hz, exchangeable with D_2O), 5.62 (d, 1H, J = 9.0 Hz), 7.37 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 54.7, 59.7, 67.5, 70.4, 71.0, 76.8, 128.3, 128.5, 128.7, 135.8, 156.2, 170.0, 170.5; IR (film) 1520, 1725, 1750, 1798, 3335 cm^{-1}; mass spectrum (EI) m/z 337 $(M)^+$, 295 $(M - Ac)^+$. Anal. Calcd for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 57.18; H, 5.75; N, 4.07.

3-[*N*-(Benzyloxycarbonyl)amino]-2-bromo-2,3-dideoxy-5-*O*-methyl-D-xylono-1,4-lactone (15). A solution of compound **12** (38 mg, 0.14 mmol) in $CHCl_3$ (2 mL) was treated successively at −20 °C under nitrogen with anhydrous LiBr (50 mg, 0.56 mmol) and boron trifluoride etherate (33 μL, 0.28 mmol). After 4 h at rt, saturated aqueous $NaHCO_3$ (5 mL) was added. Extraction of the mixture with ethyl acetate (2 × 10 mL), drying of the organic extracts over Na_2SO_4, and evaporation of the solvents *in vacuo* left a crude product which was purified by chromatography on silica gel (ethyl acetate–heptane 1:2). Compound **15** was obtained as an amorphous solid (40 mg, 80%): $[\alpha]^{22}_D$ +45.8° (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.37 (s, 3H), 3.70 (ddd, 2H, J = 1.9, 1.6, 11.6 Hz), 4.57 (d, 1H, J = 9.0 Hz), 4.73 (br d, 1H, J = 7.7 Hz), 4.94 (pseudo q, 1H, J = 8.4 Hz), 5.15 (s, 2H), 5.59 (d, 1H, J = 8.4 Hz, exchangeable with D_2O), 7.38 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.5, 59.9, 67.7, 70.8, 73.2, 78.2, 128.4, 128.6, 128.7, 158.2, 170.8; IR (film) 1530, 1720, 1788, 3330 cm^{-1}; mass spectrum (HREI) calcd for $C_{14}H_{16}NO_5{}^{79}Br$ m/z 357.0212; found 357.0200; calcd for $C_{14}H_{16}NO_5{}^{81}Br$ m/z 359.0193; found 359.0169.

General Procedures for the Opening of 2 and 12 by Alcohols. Procedure A. To a solution of **2** or **12** (0.15 mmol) in the alcohol (methanol or benzyl alcohol) was added at −30 °C boron trifluoride etherate (2.0 equiv). The reaction mixture was then stirred for 2 h at rt and saturated aqueous $NaHCO_3$ (5 mL) was added. The mixture was extracted with ethyl acetate (2 × 10 mL), the combined organic extracts were dried over Na_2SO_4, the solvents were removed under vacuum, and the crude products were purified by column chromatography on silica gel using the solvent systems indicated. Procedure B is identical in all respects to procedure A except that, at the end of the reaction period, the reaction mixture was concentrated under vacuum (bath temperature 50 °C) before the addition of saturated aqueous $NaHCO_3$. Compounds **17**–**24** were prepared by one or the other of these two procedures, as indicated.

Benzyl (2*S*,3*R*,4*S*)-4-hydroxy-2,3-imino-5-methoxypentanoate (17) and benzyl (2*S*,3*S*,4*R*)-2-acetamido-3-(ben-

zyloxy)-4-hydroxy-5-methoxypentanoate (18) were obtained from **2** and benzyl alcohol using procedure A. Elution of the chromatography column with ethyl acetate–heptane (3:1) first afforded compound **18** in 30% yield (contaminated with traces of lactone **19**, see below): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.08 (s, 3H), 3.39 (s, 3H), 3.46 (m, 1H), 3.56 (ddd, 2H, J = 10.0, 3.0, 4.1 Hz), 4.12 (dd, 1H, J = 1.6, 9.0 Hz), 4.27 (2d, 2H, J = 10.8 Hz), 5.07 (dd, 1H, J = 1.6, 8.8 Hz), 5.15 (2d, 2H, J = 12.0 Hz), 6.45 (d, 1H, J = 8.8 Hz, exchangeable with D_2O), 7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 53.4, 59.2, 67.7, 69.6, 72.7, 74.1, 79.7, 128.1, 128.4, 128.6, 128.7, 128.9, 170.8, 171.9; IR (film) 1660, 1740, 1788, 3300, 3400 cm^{-1}; mass spectrum (HRCI) calcd for $C_{22}H_{28}NO_6$ m/z 402.1916 $(MH)^+$; found 402.1935.

Continued elution of the column with ethyl acetate gave compound **17** as an oil in 35% yield: $[\alpha]^{22}_D$ −3.6° (c 0.25, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.41 (dd, 1H, J = 6.4, 7.7 Hz), 2.81 (d, 1H, J = 6.4 Hz), 3.27 (s, 3H), 3.30 (ddd, 2H, J = 5.0, 5.7, 9.7 Hz), 3.69 (ddd, 1H, J = 7.7 Hz), 5.19 (2d, 2H, J = 12.0 Hz), 7.37 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 34.1, 40.0, 59.3, 67.5, 68.7, 74.8, 128.7, 128.8, 133.4, 170.6; IR (film) 1740, 3260, 3350 cm^{-1}; mass spectrum (HRCI) calcd for $C_{13}H_{18}NO_4$ m/z 252.1236 $(MH)^+$; found 252.1264.

2-Acetamido-3-*O*-benzyl-2-deoxy-5-*O*-methyl-D-arabinono-1,4-lactone (19) was obtained in 35% yield from **2** and benzyl alcohol via procedure B and was isolated as a white solid after chromatography (ethyl acetate): mp 114 °C; $[\alpha]^{25}_D$ +39° (c 0.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.39 (s, 3H), 3.60 (dd, 1H, J = 3.8, 11.0 Hz), 3.66 (dd, 1H, J = 3.1, 11.0 Hz), 4.16 (dd, 1H, J = 5.6, 5.2 Hz), 4.48 (m, 1H), 4.62 (2d, 2H, J = 11.8 Hz), 4.66 (dd, 1H, J = 5.6, 8.3 Hz), 6.18 (d, 1H, J = 8.3 Hz, exchangeable with D_2O), 7.35 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.9, 56.1, 59.6, 71.6, 72.4, 80.2, 81.6, 128.2, 128.3, 128.7, 135.6, 164.5, 172.7; IR (film) 1540, 1665, 1788, 3300 cm^{-1}; mass spectrum (EI) m/z 293 $(M)^+$. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.22; H, 6.39; N, 4.59.

Compound **17** (30%), also isolated after continued elution of the column, was identical in all respects to that formed by procedure A, above.

Methyl (2*S*,3*R*,4*S*)-4-hydroxy-2,3-imino-5-methoxypentanoate (20) was prepared from **2** and methanol using procedure A. Chromatography of the crude material (dichloromethane–ethanol 9:1) afforded **20** as a white solid in 45% yield: mp 96–98 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.44 (dd, 1H, J = 6.4, 7.6 Hz), 2.80 (d, 1H, J = 6.4 Hz), 3.37 (s, 3H), 3.41 (ddd, 2H, J = 10.5, 5.3 Hz), 3.72 (m, 1H), 3.77 (s, 3H); IR (film) 1745, 3250, 3360 cm^{-1}; mass spectrum (CI) m/z 176 $(MH)^+$, 144 $(MH^+ - MeOH)$. Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 47.70; H, 7.01; N, 7.61.

2-[*N*-(Benzyloxycarbonyl)amino]-2-deoxy-3,5-di-*O*-methyl-D-arabinono-1,4-lactone (21) was obtained as an oil in 80% yield from **12** and methanol using procedure B and ethyl acetate–heptane (1:2) as eluent: $[\alpha]^{22}_D$ +18.2° (c 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.45 (s, 3H), 3.66 (m, 2H), 3.98 (dd, 1H, J = 5.1 Hz), 4.40 (m, 1H), 4.48 (dd, 1H, J = 8.6, 5.7 Hz), 5.15 (s, 2H), 5.55 (d, 1H, J = 8.6 Hz, exchangeable with D_2O), 7.36 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.9, 58.0, 59.6, 67.5, 71.6, 81.2, 82.3, 128.2, 128.4, 128.6, 135.8, 157.2, 171.2; IR (film) 1530, 1720, 1788, 3340 cm^{-1}; mass spectrum (EI) m/z 309 $(M)^+$. Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.05; H, 6.01; N, 4.35.

2-[*N*-(Benzyloxycarbonyl)amino]-3-*O*-benzyl-2-deoxy-5-*O*-methyl-D-arabinono-1,4-lactone (22) was obtained as an oil in 50% yield from **12** and benzyl alcohol using procedure B and ethyl acetate–heptane (1:2) for chromatography: $[\alpha]^{22}_D$ +28.1° (c 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.55 (dd, 1H, J = 2.8, 11.0 Hz), 3.63 (dd, 1H, J = 2.0, 11.0 Hz), 4.17 (t, 1H, J = 5.4 Hz), 4.45 (m, 1H), 4.54 (m, 1H), 4.55 (d, 1H, J = 11.6 Hz), 4.73 (d, 1H, J = 11.6 Hz), 5.15 (2d, 2H, J = 12.1 Hz), 5.40 (d, 1H, J = 8.4 Hz, exchangeable with D_2O), 7.31 (s, 5H), 7.36 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 57.6, 59.6, 67.7, 71.5, 72.4, 80.1, 81.3, 128.1, 128.3, 128.4, 128.5, 128.7, 132.4, 158.2, 172.2; IR (film) 1525, 1718, 1790, 3330 cm^{-1}; mass spectrum (EI) m/z 385 $(M)^+$, 294 $(M^+ - PhCH_2)$. Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.52; H, 6.13; N, 3.51.

Methyl (2*S*,3*S*,4*R*)-2-[*N*-(benzyloxycarbonyl)amino]-4-hydroxy-3,5-dimethoxypentanoate (23) was obtained from **12** and methanol via procedure A. Chromatography (ethyl acetate–heptane 2:1) of the crude reaction mixture led to concomitant partial cyclization to lactone **21** so that **23** (~15% yield) could not be obtained in pure form: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.31 (s, 3H), 3.41 (s, 3H), 3.79 (s, 3H), 3.55 (m, 2H), 4.78 (dd, 1H, J = 8.9, 1.4 Hz), 5.12 (s, 2H), 5.66 (d, 1H, J = 8.9 Hz, exchangeable with D_2O), 7.35 (s, 5H).

Isopropyl (2*S*,3*R*,4*S*)-2,3-[*N*-(benzyloxycarbonyl)imino]-4-hydroxy-5-methoxypentanoate (24) was prepared in 68% yield from **12** and isopropyl alcohol via procedure B followed by chromatography of the reaction mixture using ethyl acetate–heptane (1:2) as eluent: $[\alpha]^{22}_D$ −24.5° (c 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (2t, 6H, J = 6.3 Hz), 2.74 (m, 1H, exchangeable with D_2O), 2.89 (t, 1H, J = 6.8 Hz), 3.24 (d, 1H, J = 6.6 Hz), 3.35 (s, 3H), 3.45 (m, 2H), 3.91 (m, 1H), 5.09 (hept, 1H, J = 6.3 Hz), 5.16 (2d, 2H, J = 12.2 Hz), 7.36 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 39.4, 44.9, 59.4, 67.4, 68.9, 69.8, 73.9, 128.3, 128.5, 128.6, 135.2, 161.3, 166.5; IR (film) 1740, 3480 cm^{-1}; mass spectrum (HREI) calcd for $C_{17}H_{23}NO_6$ m/z 337.1525; found 337.1559.

(2*S*,3*R*,4*S*)-1-*N*-Benzyl-4-hydroxy-2,3-imino-5-methoxypentanamide (25). To a solution of **2** (33 mg, 0.18 mmol) in acetonitrile (5 mL) maintained at 0 °C was added benzylamine (194 μL, 1.8 mmol). The reaction mixture was stirred for 15 min at 0 ° and then concentrated under reduced pressure. The residue was purified by preparative chromatography on silica gel (ethyl acetate) yielding **25** (22 mg, 49%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40 (br s, 1H, exchangeable with D_2O), 2.50 (m, 1H), 2.90 (m, 1H), 3.34 (s, 3H), 3.42 (m, 3H), 4.40 (m, 3H, partially exchangeable with D_2O), 7.10 (br s, 1H, exchangeable with D_2O), 7.30 (m, 5H); IR (film) 1656, 3400 cm^{-1}.

(2*S*,3*R*,4*S*)-4-Acetoxy-2,3-(*N*-acetylimino)-1-*N*-benzyl-5-methoxypentanamide (26). A solution of compound **25** (20 mg, 0.08 mmol) and acetic anhydride (37 μL, 0.4 mmol) in pyridine (5 mL) was stirred at 4 °C for 12 h. The solution was concentrated *in vacuo* and the residue was purified by preparative chromatography on silica gel (ethyl acetate–heptane 2:1), yielding **26** as an oil (24 mg, 90%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.10 (s, 6H), 3.03 (t, 1H, J = 7.5 Hz), 3.31 (m, 4H), 3.50 (d, 2H, J = 3.7 Hz), 4.48 (d, 2H, J = 5.0 Hz), 4.82 (m, 1H, J = 7.5, 3.7 Hz), 6.81 (t, 1H, J = 5.0 Hz, exchangeable with D_2O), 7.30 (m, 5H); mass spectrum (EI) m/z 334 $(M)^+$. Anal. Calcd for $C_{17}H_{22}N_2O_5 \cdot {}^3/_4CH_3CO_2C_2H_5$: C, 60.00; H, 7.00; N, 7.00. Found: C, 60.17; H, 7.32; N, 7.25.

(2*S*,3*R*,4*S*)-1-*N*-Benzyl-2,3-[*N*-(benzyloxycarbonyl)imino]-4-hydroxy-5-methoxypentanamide (27). By following the same procedure as for the preparation of **25**, lactone **12** (46 mg, 0.17 mmol) reacted with benzylamine (180 μL, 1.66 mmol) in acetonitrile (4 mL) to give, after 1.5 h at 10 °C followed by workup, compound **27** as a white solid (30 mg, 47%): mp 83 °C; $[\alpha]^{25}_D$ −37.8° (c 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.74 (m, 1H, exchangeable with D_2O), 2.90 (t, 1H, J = 7.2 Hz), 3.26 (d, 1H, J = 7.2 Hz), 3.34 (s, 3H), 3.45 (m, 2H), 3.50 (m, 1H), 4.40 (oct, 2H, J = 5.7, 6.2, 14.6 Hz), 5.13 (s, 2H), 6.75 (t, 1H, J = 5.7 Hz, exchangeable with D_2O), 7.20–7.36 (m, 10H); IR (film) 1540, 1662, 1731, 3330, 3380 cm^{-1}; mass spectrum (EI) m/z 384 $(M)^+$, 293 $(M - PhCH_2)^+$. Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.42; H, 6.07; N, 7.13.

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