Preparation of β-Substituted Tryptophan Derivatives: Comparison of the Reactivity of *N*-Methylindole toward Aziridine-2-lactones and Aziridine-2-carboxylic Esters and Interpretation of Results Using MNDO Calculations

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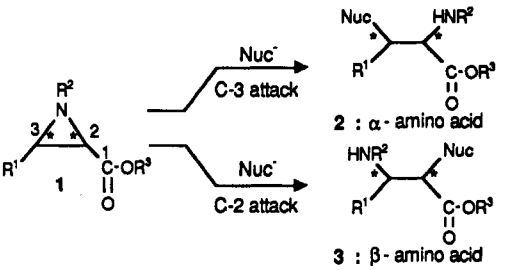
With the aim of preparing novel β-functionalized tryptophan derivatives, the reaction of (1*S*,4*S*,5*R*)-*N*-acetyl-4-(methoxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**4**), a newly developed rigid analogue of the synthetically useful aziridine-2-carboxylic esters of type **1**, with *N*-methylindole (**6**) was studied under acidic (Lewis acid) conditions. *N*-Methylindole reacted exclusively at C-2 of **4** to give 3-acetamido-2,3-dideoxy-2-*C*-[3-(1-methylindolyl)]-5-*O*-methyl-D-xylonolactone (**7**) in contrast to this nucleophile's known reactivity with aziridine-2-carboxylic esters **1** at C-3 under the same conditions. The desired β-substituted tryptophan derivative **12** was instead obtained by reacting **6** with the *tert*-butyldimethylsilyl furanoside precursor of **4** (i.e., **9**) followed by desilylation and oxidation of the anomeric hydroxyl function with TPAP. The regioselectivity of aziridine ring opening by **6** was rationalized by comparison of the LUMO coefficients and atomic charge distributions for the reactive centers of the aziridine-2-lactone **4**, the aziridine-2-carboxylic ester **16**, and the aziridine furanoside **9** in both their ground states and protonated states as determined using MNDO calculations. It was found that (1) protonation of both **4** and **16** causes a large increase in the LUMO coefficients at C-2 and C-3, thereby directing attack by *N*-methylindole (**6**), a soft nucleophile, toward these centers via orbital control, as has been experimentally observed; (2) of C-2 and C-3, the higher LUMO coefficient was found at the former position for the N-protonated forms of both **4** and **16**, suggesting that C-2 is the preferred site of attack by **6** in both cases. Though this was verified experimentally in the case of lactone **4**, the fact that aziridine-2-carboxylic esters (e.g. **16**) always react with indoles at C-3 under acidic conditions indicates that in these compounds, steric and/or electrostatic effects rather than orbital considerations determine the course of the reaction; (3) in the case of the N-protonated aziridino furanoside **9**, C-3 was calculated to have a higher LUMO coefficient than C-2, in accord with the exclusive attack of **6** at the former position. MNDO calculations thus appear to be a useful tool for the prediction of the reactivity patterns of rigid aziridine structures such as **4** and **9**, but are less satisfactory in the case of flexible aziridine-2-carboxylates in which other factors may predominate.

Introduction

The use of aziridine-2-carboxylates **1** as intermediates in the synthesis of optically active amino acids, both natural and unnatural, is a subject of much current interest (Scheme 1).[1-11] While the reactivity of **1** (R^2 = H) is relatively low, activation can be obtained by incorporation of an electron-withdrawing group on the nitrogen atom (e.g., R^2 = acyl, carbamyl, sulfonyl) and/or by use of acidic reaction conditions. Nucleophiles which have been reported to effect such aziridine ring opening by attack at C-3 (the most commonly encountered situation and which yields α-amino acids **2**) include alcohols,[2,10] thiols,[3,9,11] amines,[1] Wittig reagents,[4] and indole derivatives[6,7,9] while organocuprates[5] and malonates[8] have been observed to give mixtures of C-2 (i.e., β-amino acids **3**) and C-3 addition products.

Scheme 1



In the particular case of indole as nucleophile, β-substituted tryptophans are formed. Thus, β-methyltryptophan (**2**, R^1 = CH_3; Nuc = 3-indolyl), a naturally occurring, biologically active nonproteinaceous amino acid[12] and a structural unit or precursor of several anti-

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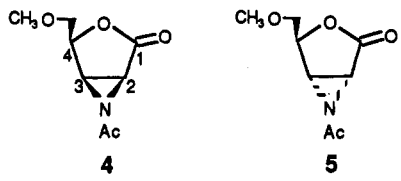
tumor antibiotics (e.g., telomycin,[13,14] streptonigrin,[15,16] lavendamycin[17]) has been prepared with complete stereocontrol of both chiral centers starting from 1 ($R^1 = CH_3$).[7] Although two other methodologies (both based on 1,4-Michael additions of simple organocuprates to α,β-dehydrotryptophan precursors) have recently been published which also permit stereospecific preparation of β-alkyltryptophans,[18] the introduction of a functional group at the β-position has never been described. Such a functional group would be useful in elaborating an array of β-substituted tryptophan derivatives for biological evaluation.

With this purpose in mind, we have recently synthesized the aziridine-2-lactones 4 and 5 starting from D-ribose and D-lyxose, respectively.[19] These compounds may be considered as rigid, bicyclic analogues of 1 carrying three stereochemically defined chiral centers (i.e., C-2, C-3, and C-4) (carbohydrate numbering). For the preparation of novel tryptophan derivatives, these lactones present the advantage of providing protection for the carboxylic acid function of tryptophan and, upon hydrolysis, of liberating a vicinal diol group at the β-position which can be further transformed. Moreover, these lactonized tryptophans are pharmacologically interesting in themselves since they and the β-carbolines which may be prepared from them display CNS activity.[20] We report herein our results in this direction. Furthermore, the unexpected reactivity of aziridine-2-lactones 4 and 5 has prompted us to attempt

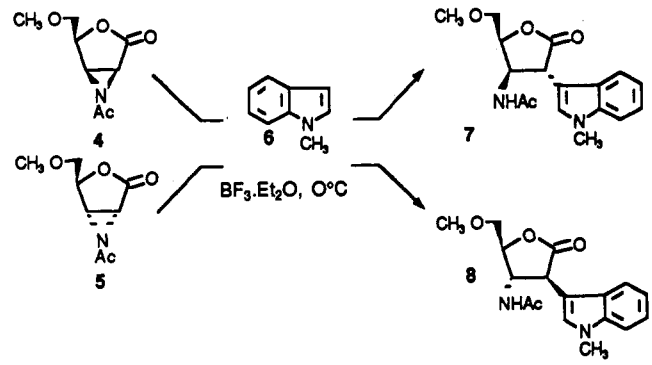


to interpret the reactivity of these molecules, as well as of aziridine-2-carboxylates 1, toward indole using perturbational and HSAB (hard and soft acids and bases) theories.[21,22] This approach was recently used by Font and co-workers[23] to rationalize the diverse behavior of conjugated oxiranes toward nucleophiles.

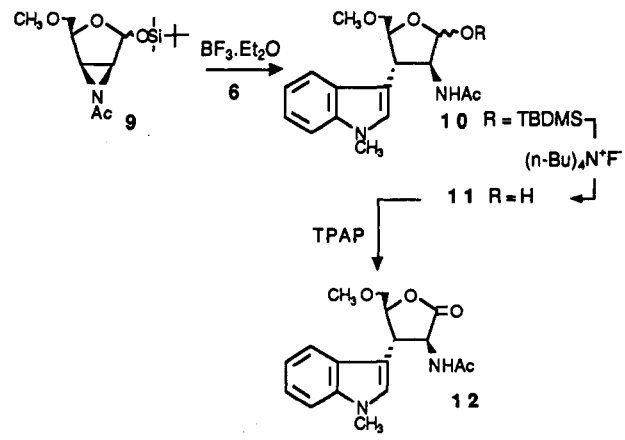
Results

The Lewis acid-catalyzed condensation of indole derivatives with activated aziridine-2-carboxylates of type 1 has been used to prepare tryptophan,[6] β-methyl tryptophan,[7] and β-phenyltryptophan,[9] stereospecifically. In these cases, the C-3 position of indole has invariably been

Scheme 2



Scheme 3



found to attack the C-3 position of the aziridine to give the desired tryptophan derivative. It was thus with some surprise that under these same conditions, the reaction of *N*-methylindole (6) with either aziridine-2-lactones 4 or 5 in the presence of boron trifluoride etherate yielded exclusively compounds 7 and 8, respectively, corresponding to nucleophilic attack of C-3 of indole to *C-2* of the aziridines (Scheme 2). The ^{1}H-NMR spectra of 7 and 8 being very similar, conclusive structural assignments were obtained by NOESY experiments. Thus, for compound 8, H-3 was correlated with the 5-*O*-methyl group while H-4 was correlated with H-2. Such a pattern is only compatible with a dideoxyarabino arrangement of the C-2 and C-3 substituents (indole and acetamide, respectively), in turn the result of attack of the indole at C-2 of the aziridine-2-lactones. Furthermore, the fact that complete inversion of configuration was observed at C-2 suggests that a clean S_N2 process is involved in opening of this aziridine ring.[7,9,24]

That *N*-methylindole had not added to the C-3 position of aziridine 4 was confirmed by the unambiguous preparation of the C-3 addition compound 12 (Scheme 3). Thus, condensation of *N*-methylindole (6) with the *tert*-butyldimethylsilyl 2,3-iminoribofuranoside 9[19] in the presence of boron trifluoride etherate gave the 2-acetamido-2,3-dideoxy-3-*C*-[3-(1-methylindolyl)]arabinofuranoside 10 as an α,β mixture. The latter was desilylated with fluoride anion and the resulting free anomeric hydroxyl group (i.e. 11) was oxidized by use of tetrapropylammonium perruthenate (TPAP), yielding lactone 12. The ^{1}H-NMR spectrum of 12, clearly different from that of its isomer 7, was sufficiently resolved to allow precise struc-

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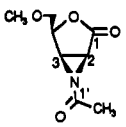
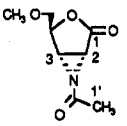
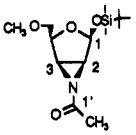
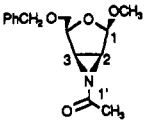
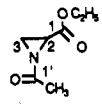
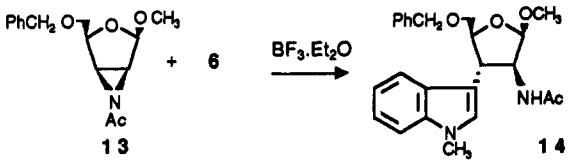
Table 1. LUMO Coefficients and Atomic Charge Distributions, as Calculated Using MNDO, for the Four Electrophilic Centers of *N*-Acetylaziridine-2-carboxylates and Related Furanosides in their Ground States and N-Protonated (N^+) States

compounds				LUMO coefficients[a] (charge distribution)			
structure	no.	LUMO energy (eV)	entry	C-1	C-2	C-3	C-1′
	4	0.21	1	0.12	0.12	0.02	0.35
			2	(+0.37)	(−0.03)	(+0.005)	(+0.32)
	4-N^+ [c]	−5.22	3	0.032	0.23	0.09	0.22
			4	(+0.32)	(+0.02)	(+0.05)	(+0.32)
	5	0.16	5	0.11	0.11	0.02	0.36
			6	(+0.36)	(−0.02)	(+0.01)	(+0.32)
	5-N^+ [c]	−5.34	7	0.03	0.22	0.11	0.20
			8	(+0.31)	(+0.01)	(+0.06)	(+0.32)
	β-9	0.83	9	0.001	0.09	0.01	0.52
			10	(+0.40)	(−0.01)	(−0.03)	(−0.31)
	β-9[c]	0.83	11	0.005	0.01	0.09	0.51
			12	(+0.34)	(−0.02)	(+0.02)	(+0.31)
	β-9-N^+ [c]	−4.41	13	0.005	0.06	0.10	0.23
			14	(+0.34)	(−0.01)	(+0.04)	(+0.32)
	13[b]	0.26	15	0.001	0.08	0.01	0.52
			16	(+0.33)	(−0.03)	(−0.01)	(+0.32)
	13[b,c]	0.17	17	0.001	0.01	0.09	0.52
			18	(+0.33)	(−0.02)	(−0.02)	(+0.31)
	13-N^+ [c]	−4.51	19	0.002	0.03	0.28	0.27
			20	(+0.32)	(−0.01)	(+0.05)	(+0.32)
	16	0.52	21	0.079	0.03	0.01	0.41
			22	(+0.39)	(+0.02)	(+0.10)	(+0.32)
	16-N^+ [c]	−5.06	23	0.006	0.23	0.13	0.23
			24	(+0.36)	(+0.06)	(+0.13)	(+0.32)

[a] The coefficients correspond to $\sum c^2$ of the atomic valence orbitals of each atom. The roots are the eigenvalues or energy levels in electron volts (eV) of the molecular orbitals. [b] LUMO-2 coefficients are reported since LUMO and LUMO-1 coefficients were centered on the benzene ring. [c] Results of calculations for structures having acetyl carbonyl turned 180° to that depicted.

Scheme 4



tural assignment after a NOESY experiment. Thus, H-3 was correlated with the 5-*O*-methyl group as well as with the amide NH.

In order to eliminate the possibility that the bulky (α,β)-*tert*-butyldimethylsilyl group does not affect, on steric grounds, the regioselectivity of *N*-methylindole addition to aziridine **9**, and also to simplify MNDO calculations (see below), this reaction was repeated with the β-1-*O*-methylaziridine **13**[19] (Scheme 4). Thus, treatment of the latter with *N*-methylindole (**6**) and boron trifluoride etherate yielded, again, exclusively the product corresponding to opening of the aziridine ring at C-3 of the furanoside (**14**). The resulting *cis* arrangement of H-1 and H-2 was indicated by a coupling constant of 4.5 Hz between these two protons. The structural assignment of **14** was completely corroborated by its NOESY spectrum which displayed clear correlations between H-3 and H-5 as well as between H-3 and the amide NH.

Computational Methods

The recent version of Insight II (2.1.0., March 1992) was used on a Silicon Graphics workstation for the molecular modeling of structures. The structures were built with Insight and then initial geometries were corrected by use of the Discover program (available in Insight II-Discover 2.0) using no cross terms and no Morse term for 3500 iterations for each structure and using conjugate gradients until maximum derivatives of less than 0.001 kcal/Å were obtained. The semiempirical quantum mechanical MNDO method implemented in MOPAC 6.00 was used for the final optimization of structures. MNDO[25] optimizations were performed on internal coordinates using the default optimizer until SCF field was achieved. The combination of two optimization methods (i.e., from Discover and from MOPAC) can be expected to minimize errors in the localization of minima. The geometry of all the structures (bond distances, bond angles, and dihedral angles) were fully optimized using restricted Hartree–Fock (RHF) calculations. The Z matrix for all the computed structures are available from the authors. The partial charges (Mulliken populations) were retrieved directly from MOPAC results.

Though boron trifluoride etherate was used in all the experiments, MOPAC calculations were simplified by simulating this Lewis acid's coordination at the aziridine ring nitrogen by the approach of a proton toward this atom.[26] Full geometry minimizations of these intermediates were performed and the charge distributions and LUMOs were obtained for each aziridine structure in both its ground state (general structure **15**) (Figure 1) and its N-protonated state (**15**-N^+). Values are given in Table 1. The alternative structure for the protonated form of the aziridine, in which the oxygen of the acetyl group is protonated (i.e., general structure **15**-O^+) instead of the

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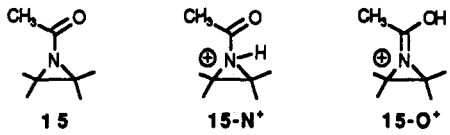


Figure 1. General representation of *N*-acetylaziridines in the ground state (**15**) and in their protonated states (**15**-N$^+$: N-protonation, **15**-O$^+$: O-protonation).

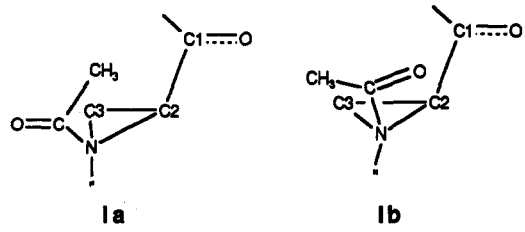


Figure 2. Two alternative rotamers of the *N*-acetyl group of the ground-state aziridine substrates considered for MOPAC calculations. Rotamers **Ia** and **Ib** are of equivalent energy for compounds **4**, **5**, and **16** while rotamer **Ib** is 0.4 kcal lower in energy than rotamer **Ia** for compounds **9** and **13**.

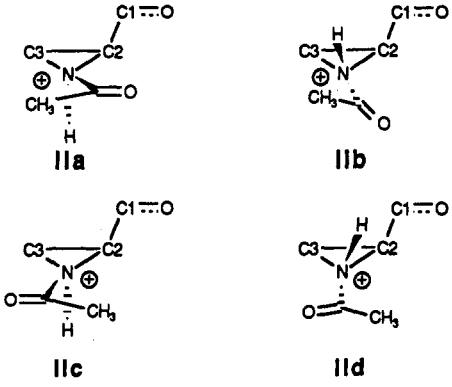


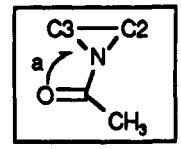
Figure 3. Alternative geometries for the N-protonated *N*-acetylaziridines. Structure **IIa** is at least 2.5–3.5 kcal lower in energy than **IIb–d**.

nitrogen atom was also considered. This point will be discussed in more detail below.

In the ground state, both rotameric forms of the acetyl group of compounds **4**, **5**, and **16** (i.e., structures **Ia** and **Ib**, Figure 2) had the same calculated heats of formation. In the case of compounds **9** and **13**, conformer **Ib** (i.e., with the acetyl carbonyl oxygen on the same side as C-2) was favored over conformer **Ia** but only by 0.4 kcal. For this reason, and because ^{1}H NMR spectra of the ground-state substrates did not indicate the presence of rotameric mixtures, charge distributions and LUMO coefficients are given in all cases for substrates having conformation **Ia** (Table 1). In the case of compounds **9** and **13**, these values are also given, for the sake of comparison, for geometries corresponding to conformer **1b** (entries 11, 12, 17, and 18). It can thus be seen that in the ground state, the rotameric form of the acetyl group has little effect on the calculated LUMO coefficients and charge distributions at the atoms considered.

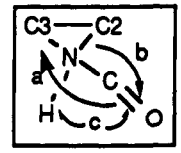
The situation is somewhat more complex in the case of the protonated substrates since both the position of the acetyl group and of the proton must be considered (Figure 3). The combined Discover and Insight programs gave structure **IIa** as the lowest energy conformation (i.e., the acetyl carbonyl oxygen on the same side as C-2 and the proton *s-cis* to the carbonyl oxygen). However, the

Table 2. Calculated Dihedral Angles for the Minimized *N*-Acetylaziridine Structures in the Ground State and the N-Protonated State



Ground state

Compounds	4	5	β–9	13	16
Dihedral Angle (°)					
O-C-N-C3 (a)	-33.3	-28.6	-31.7	-27.9	-32.4



N-Protonated state

Compounds	4-N$^+$	5-N$^+$	β–9-N$^+$	13-N$^+$	16-N$^+$
Dihedral Angle (°)					
O-C-N-C3 (a)	-168.4	-167.5	-167.5	-167.6	-167.3
O-C-N-C2 (b)	117.0	118.3	118.6	118.3	117.5
O-C-N-H (c)	-19.6	-18.6	-18.5	-18.8	-20.0
H-N-C2-C1	-15.1	-14.1	-14.4	-14.6	-9.9

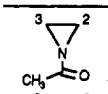
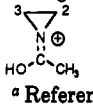
alternate structures **IIb–d** were also considered. Thus, structure **IIb**, in which the proton is now *s-trans* to the acetyl carbonyl oxygen, was calculated to have a heat of formation of 3.5 kcal greater than **IIa**. Turning the carbonyl group 180° (i.e. the oxygen atom of the acetyl carbonyl now on the same side as C-3) while maintaining the proton in an *s-cis* position (structure **IIc**) also gives structures requiring higher heats of formation. Thus, for protonated compounds **4**, **13**, and **16**, the heats of formation of the **IIc** geometries are respectively 3.2, 2.5, and 3.2 kcal greater than those of their **IIa** geometries. Finally, structure **IId**, which cumulates both an unfavorable carbonyl conformation and an *s-trans* proton, was not considered further. Charge distributions and LUMO coefficients were thus in all cases calculated for protonated substrates having geometries corresponding to **IIa** (i.e., Table 1, acetyl carbonyl turned 180° from the structures depicted). The full geometries of the ground state and N-protonated *N*-acetylaziridines of each substrate studied are given in Table 2.

The validity of MNDO calculations on aziridines has previously been demonstrated, particularly with respect to lone-pair repulsions and strain energies in these systems.[27,28] In order to validate our own results, we compared the bond lengths and bond angles of aziridines obtained by MNDO calculations with those obtained by X-ray determinations (Table 3).[29] In both cases, the corresponding internuclear distances of the aziridine nuclei obtained by calculation and from X-ray data were identical within ±0.02 Å and bond angles were comparable.

In all cases, the calculated LUMO energies of the protonated aziridines (i.e. of type **15**-N$^+$) were lower than

(27) Wurthwein, E.-U. *J. Org. Chem.* **1984**, *49*, 2971.
(28) Jennings, W. B.; Worley, S. D. *J. Chem. Soc. Perkin Trans. 2* **1980**, 1512.
(29) A systematic search was performed using the Cambridge structural database (1989, version 3.4), Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge, U.K.
(30) Trefonas, L. M.; Towns, R.; Majeste, R. *J. Heterocycl. Chem.* **1967**, *4*, 511.
(31) Shirahata, K.; Hirayama, N. *J. Am. Chem. Soc.* **1983**, *105*, 7199.

Table 3. Comparison of the Internuclear Distances and Bond Angles of Protonated and Nonprotonated Aziridines Determined by Calculation and by X-ray Diffraction

	internuclear distances (Å)			bond angles (deg)		
	bond	X-ray[a]	calcd[b]	bond	X-ray	calcd
	$N-C_2$	1.49	1.48	C_2-N-C_3	60.46	62.10
	$N-C_3$	1.46	1.46	C_2-C_3-N	60.60	59.06
	C_2-C_3	1.48	1.49	$N-C_2-C_3$	58.94	58.73
	$N-C_2$	1.51[c]	1.52	C_2-N-C_3	60.61	69.52
	$N-C_3$	1.51[c]	1.53	C_2-C_3-N	59.78	55.27
	C_2-C_3	1.52[c]	1.51	$N-C_2-C_3$	59.70	55.27
	$N-C_2$		1.48	C_2-N-C_3		63.51
	$N-C_3$		1.48	C_2-C_3-N		58.05
	C_2-C_3		1.53	$N-C_2-C_3$		58.40

[a] References 30 and 31. [b] Calculated for compound 4 using MOPAC as described in the text. [c] X-ray data for a quaternized *N,N*-dimethylaziridine.

those in the ground state (e.g. **15**) consistent with the enhanced reactivity of the former toward nucleophiles. Furthermore, as can be seen from Table 1, protonation also produced a significant increase in the LUMO coefficients of the aziridine carbon atoms (C-2 and C-3).

Interpretation of Experimental Results

It is difficult to generalize the diverse behavior of aziridine rings of type **1** toward nucleophiles as a function of a single factor. Regioselectivity and rate of opening of simple aziridine rings (i.e., having no 2-carboxy function) have been studied as functions of the leaving group quality of the substituted nitrogen atom,[32,33] of the geometry of the nitrogen atom and its lone pair of electrons,[32,34] of steric[32,35] and benzylic[32,35,36] effects, and of the ring substituents.[24,37] The hard–soft character of nucleophiles has been observed to affect the regioselectivity of their attack at either the carbonyl function or the ring carbons of unsubstituted aziridine-*N*-carbamates.[38] The effect of ring substituents on the regioselectivity of nucleophilic attack on aziridine-2-carboxylates has received limited attention.[8] Such regioselectivity has also been observed to vary with the nature of the nucleophile,[1,5] but no generalizations have been put forward which would allow predictions to be made. In the present case, the unexpected regioselectivity of attack of *N*-methylindole at C-2 of aziridine-2-lactones (as opposed to attack at C-3 of aziridine-2-carboxylates) may be rationalized in terms of perturbational/HSAB theories. Thus, on the basis of the Klopman–Salem equation, both Coulombic and molecular orbital interactions between a nucleophile and a substrate influence the outcome of the reaction.[22] In particular, it is the occupied molecular orbitals of the nucleophile which should interact with the unoccupied molecular orbitals of the aziridines. Moreover, the reactivity of a hard nucleophile will be under charge control while that of a soft nucleophile will be under orbital control. The calculated atomic charge distributions and LUMOs (the only orbital treated in the present case) of the various aziridine substrates considered and their N-protonated derivatives (designated as N^+) are given in Table 1.

Aziridine lactone **4** in the ground state shows only a minor contribution by C-2 and C-3 atomic orbitals to the LUMO (entry 1). However, Lewis-acid activation of the aziridine-2-lactone **4**, to give **4**-N^+ (entry 3), produces a significant modification of the LUMO parameters. Calculations show that in the protonated species **4**-N^+ (in which the coordination of boron trifluoride etherate with the aziridine nitrogen atom has been simulated by simple protonation at this site) the LUMO coefficients at C-2 and C-3 have increased with respect to the unprotonated species while the LUMOs of the two carbonyl groups (C-1, C-1′) have decreased. *The largest LUMO coefficient is now, in fact, at C-2 (0.23) and the latter should thus be the preferred site of attack of N-methylindole (**6**), a soft nucleophile, whose reactivity is under orbital control.* This is clearly corroborated by our experimental findings (Scheme 2). Although the LUMO coefficient of the acetyl carbonyl group of **4**-N^+ is only very slightly smaller than that at C-2 (0.22 vs 0.23), steric hindrance due to proximal boron trifluoride etherate coordination may explain the observed lack of reactivity of the acetyl group toward the nucleophile. Nucleophilic attack at C-2 rather than at the acetyl group has the added advantage of providing relief of ring strain.

As remarked upon above, the usual mode of attack by nucleophiles (including indoles) of protonated *N*-acylaziridine-2-carboxylates (e.g. **16**-N^+) has been observed to occur at C-3. Since aziridine-2-lactone **4**-N^+ apparently gives exclusively the product of C-2 attack, we thought it worthwhile to compare the LUMO coefficients and charge distributions of **4**-N^+ (entry 3) with those of the monocyclic aziridine **16**-N^+ (entry 23). Interestingly, these two parameters were almost identical for C-2 and C-3 of these two aziridines. This result implies that indoles (e.g., **6**), which are soft nucleophiles and whose reactivity is under orbital control, should normally attack **16**-N^+ at C-2 in preference to C-3. The fact that this has never been observed experimentally[6,7,9] suggests that, for **16**-N^+, steric considerations may override orbital considerations in determining regioselectivity of attack, the least-hindered position being, in fact, C-3. Locking the ester function into a lactone ring thus appears to diminish steric hindrance at C-2, allowing orbital factors to determine regioselectivity of attack. Nucleophilic attack at C-2 of the aziridine esters may also be inhibited by repulsion between the incoming nucleophile and the negative charges of the neighboring oxygen atoms. The fact that, in the rigid aziridine lactones, these negative charges are positioned away from the direction of nucleophilic approach again allows orbitally-favored C-2 attack to occur. This argument has previously been used to rationalize preferential C-2 attack of isoelectronic 2-carboxyoxiranes by nucleophiles under acidic conditions.[23]

The aziridine-2-carboxylate and lactone systems may also be seen as being analogous to α-chloro carbonyls in which the carbonyl function (ketone or ester) has been observed to greatly accelerate the rate of S_N2 displacement of chloride by nucleophiles.[39] Early work by Bartlett[39d] as well as more recent *ab initio* calculations by Bach and co-workers[40] have shown that this acceleration is very much dependent on the ground-state conformation of the

(32) Buchholz, B.; Stamm, H. *Isr. J. Chem.* **1986**, *27*, 17.
(33) Kozikowski, A. P.; Ishida, H.; Isobe, K. *J. Org. Chem.* **1979**, *44*, 2788.
(34) Mall, T.; Stamm, H. *J. Org. Chem.* **1987**, *52*, 4812.
(35) Stamm, H.; Speth, D. *Chem. Ber.* **1989**, *122*, 1795.
(36) Onistschenko, A.; Buchholz, B.; Stamm, H. *Chem. Ber.* **1986**, *119*, 2678.
(37) Takeuchi, H.; Koyama, K. *J. Chem. Soc. Perkin Trans. 2* **1981**, 121.
(38) (a) Hassner, A.; Kascheres, A. *Tetrahedron Lett.* **1970**, 4623. (b) Stamm, H. *Tetrahedron Lett.* **1971**, 1205.

substrate. The most energetically favorable conformation for such acceleration (i.e. the conformation most resembling that of the transition state) was determined to be the one in which the carbonyl function is turned 90° to the chloride. This is, in fact, precisely the conformation which the lactone carbonyl is forced to adopt with respect to the departing *N*-acetyl group in the rigid aziridine-2-lactones **4** and **5**. The exclusive reaction of *N*-methylindole (**6**) at C-2 of these lactones may thus be seen as an illustration of orbitally driven conjugate acceleration of S_N2 displacement at this position.[41] The aziridine-2-carboxylates **16** can also adopt this favored conformation by rotation about the C1–C2 bond, but this may be energetically expensive (e.g., for steric reasons) so that the alternative possibility of C-3 attack by *N*-methylindole is observed.

This reactivity of aziridine-2-lactones is confirmed by the only other known example of this type in which the aziridine ring of the 5-*O*-acetyl analogue of **4** was opened by hydrazoic acid to give the 2-azido-2-deoxy reaction product.[42] This result is consistent with that predicted by our molecular orbital calculations.

As determined experimentally, the *N*-acetyl-2,3-aziridine silyl and methyl furanosides (**9** and **13**, respectively) react with *N*-methylindole in the presence of boron trifluoride etherate to give exclusively the products of N–C-3 bond opening (**10** and **14**), in direct contrast to the lactone analogues which, as discussed above, gave only the products of N–C-2 bond opening. An explanation for this inversion of reactivity in the furanosides is, in fact, evident from their calculated LUMO coefficients. In both cases, the C-3 positions of aziridine furanosides **9**-N^+ (β anomer) and **13**-N^+ (entries 13 and 19, respectively) have significantly higher coefficients (0.10 and 0.28, respectively) than the C-2 positions (0.06 and 0.03) and the former should thus be the preferred site of reaction of a soft base such as *N*-methylindole. Although the difference between the LUMO coefficients for C-3 and C-2 of the *O*-silyl derivative **9**-N^+ was not as pronounced as for the methyl furanoside **13**-N^+, this may be the result of acknowledged discrepancies which have been observed when MNDO calculations are applied to silicon-containing molecules.[43] As with lactones **4**-N^+ and **5**-N^+, the acetyl groups of **9**-N^+ and **13**-N^+ have LUMO coefficients of the same order as C-3; however, reaction at these positions is inhibited for the same reasons as discussed above in relation to **4**-N^+.

Finally, the present findings may help to shed some light on the site of protonation of *N*-acylaziridines in acidic medium. The problem of *O*- vs *N*-protonation of amides in general has often been addressed but has not yet been definitively resolved. However, spectroscopic evidence (NMR, IR, UV, in particular) appears to favor O-protonation.[44] In the case of *N*-acylaziridines, both possibilities (i.e., **15**-N^+ and **15**-O^+, Figure 1) have been used to rationalize the regioselectivities of ring opening (i.e., C-2 vs C-3 attack) by nucleophiles under acidic conditions.[24,26,45] Recent work by Lin and co-workers[24,45] pointed to O-protonation on the basis of product distribution using various aziridine substrates. On the other hand, both O- and N-protonated forms of *N*-acylaziridines have been detected by NMR by Olah.[46] It was suggested that these two tautomeric forms exist in equilibrium, with the O-protonated species predominating. In view of this possibility, we calculated the LUMO coefficients of the O-protonated forms of an *N*-acylaziridine lactone (**4**-O^+) and carboxylate (**16**-O^+) (Figure 4). The LUMO coefficients on C-2 and C-3 of both **4**-O^+ and **16**-O^+ were found to be very small compared to those of their N-protonated forms (entries 3 and 23, Table 1). Such small LUMO coefficients at C-2 and C-3 could not account, on the basis of HSAB theory, for the observed reactivities of soft nucleophiles at these centers. A further indication that the N-protonated form is the reactive species in these reactions comes from calculations of bond lengths. Thus, while O-protonation modestly increases only the N–C-3 bond length compared to nonprotonated substrate (Table 3), N-protonation results in significant lengthening of both N–C-2 and N–C-3. Since bond lengthening is indicative of bond weakening, the N-protonated aziridines should reasonably be expected to be more susceptible to nucleophilic ring opening than their O-protonated forms.[47] These results would tend to suggest that while both N- and O-protonated forms of *N*-acetylaziridine-2-carboxylates (and lactones) may exist in equilibrium in solution (as shown by Olah[46]), it is the former species which is the more reactive toward opening of the aziridine ring by soft nucleophiles.

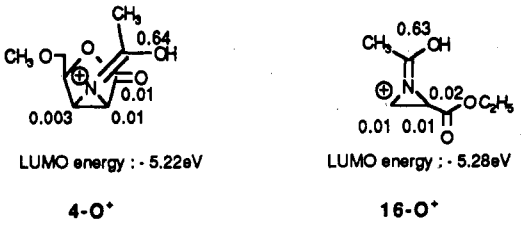


Figure 4. LUMO coefficients for the alternative O-protonated forms of **4** and **16**.

Conclusion

The present study shows that *N*-methylindole, known to react at the C-3 position of aziridine-2-carboxylates of type **1**, reacts exclusively at the C-2 position of aziridine-2-lactones of type **4**. This unexpected regioselectivity can, moreover, be rationalized by consideration of the LUMO coefficients of the reactive centers of the substrate. The MNDO approach also provides an explanation, in orbital terms, for several experimental observations concerning aziridine reactivity. Firstly, the increased reactivity of

(39) See for example: (a) Bordwell, F. G.; Brannen, W. T. *J. Am. Chem. Soc.* **1964**, *86*, 4645. (b) Sisti, A. J.; Lowell, S. *Can. J. Chem.* **1964**, *42*, 1896. (c) Halvorsen, A.; Songstad, J. *J. Chem. Soc. Chem. Commun.* **1978**, 327. (d) Bartlett, P. D.; Trachtenberg, E. N. *J. Am. Chem. Soc.* **1958**, *80*, 5808.

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(41) We thank a referee for pointing this out.

(42) Egli, M.; Dreiding, A. S. *Helv. Chim. Acta* **1986**, *69*, 1442.

(43) Verwoerd, W. S. *J. Comput. Chem.* **1982**, *3*, 445.

(44) For a review of this subject, see: Homer, R. B.; Johnson, C. D. Acid-Base and Complexing Properties of Amides. *The Chemistry of Amides*; Zabicky, J. Patai, S., Eds.; Wiley Interscience; London, 1970; pp 187–197.

(45) Lin, P.-Y.; Bentz, G.; Stamm, H. *J. Prakt. Chem.* **1993**, *335*, 23.

(46) Olah, G. A.; Szilagyi, P. J. *J. Am. Chem. Soc.* **1969**, *91*, 2949.

(47) Lin and co-workers[45] have used the same argument to explain the increased reactivity of O-protonated *N*-acylaziridines with respect to nonprotonated *N*-acylaziridines. However, these authors did not consider the effect of N-protonation on bond lengthening which, as we now show, is even more pronounced. It was also argued that ring opening of these aziridines is favored by a flattened nitrogen pyramid (planarization effect) and the resulting increase in ring strain which is maintained by O-protonation. However, the aziridine-2-lactones considered here (in contrast to the simple aziridines considered by Lin) are already in a highly strained state due to their fused, bicyclic nature so that the additional strain which would result from O-protonation and planarization may be an unfavorable process, and N-protonation may thus predominate.

N-acylated aziridines under acidic conditions is due to a general decrease in the LUMO energy of this species as compared to the ground-state molecule. Secondly, protonation (or Lewis acid coordination) of the aziridine ring directs nucleophilic attack toward the carbon atoms of the ring (C-2, C-3) due to the greatly enhanced LUMO coefficients at these centers compared to ground state. Thirdly, the observed correlations between LUMO coefficients and reactivity of *N*-acylaziridines under acidic conditions suggest that the reactive intermediate is the N-protonated (or Lewis acid coordinated) species rather than the O-protonated species.

Finally, while the direct attack of indole on aziridine-2-lactones does not allow access to β-substituted tryptophan derivatives as initially projected, the latter can be efficiently synthesized by reaction of indole with iminofuranosides followed by oxidation of the anomeric hydroxyl function (Scheme 3). Extension of these results to the preparation of pharmacologically active substances is in progress.

Experimental Section

General. Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra of samples were obtained either as KBr pellets (for solids) or as films (for oils) with a Nicolet 205 FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were determined on a Bruker WP200 MHz, Bruker WP250 MHz, or Bruker AM300 MHz instrument. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization mass spectra were recorded on an AEI MS-50 and AEI-MS-9 spectrometer, respectively. FAB spectra and high-resolution mass spectra were recorded on a Kratos MS 80RF instrument. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. 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). Acetonitrile was distilled from P_2O_5 and kept over 4-Å molecular sieves. Boron trifluoride etherate, TPAP, *N*-methylindole, and 4-methylmorpholine *N*-oxide were purchased from Aldrich Chemical Co. and were used without further purification. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

3-Acetamido-2,3-dideoxy-2-*C*-[3-(1-methylindolyl)]-5-*O*-methyl-D-xylonolactone (7). To a solution of aziridine **4** (36 mg, 0.19 mmol) in *N*-methylindole (**6**, 51 μL, 0.38 mmol) at 0 °C under nitrogen was added boron trifluoride etherate (25 μL, 0.19 mmol). After 10 min, ethyl acetate (10 mL) was added to the solidified reaction mixture. The solution was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL), the organic phase was dried over Na_2SO_4, and the solvents were removed *in vacuo*. The crude product was purified by preparative chromatography on silica gel (ethyl acetate), yielding unreacted starting material **4** (10 mg, 28%) and compound **7** (18 mg, 29%; 41% based on consumed starting material) as a white foam: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.49 (s, 3H), 3.72 (m, 5H), 4.20 (d, 1H, *J* = 10.0), 4.80 (d, 1H, *J* = 10.0), 5.20 (q, 1H), 6.36 (d, 1H, exchangeable with D_2O), 6.98 (s, 1H), 7.14 (t, 1H), 7.26 (m, 2H), 7.65 (d, 1H); IR (neat) 1659, 1776, 3368 cm^{-1}; mass spectrum (EI), *m/z* 316 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.55; H, 6.32; O, 20.25. Found: C, 64.41; H, 6.69; O, 20.45.

3-Acetamido-2,3-dideoxy-2-*C*-[3-(1-methylindolyl)]-5-*O*-methyl-D-arabinonolactone (8). Following the same procedure as for the preparation of **7**, the title compound was obtained from aziridine-2-lactone **5** in 35% yield after chromatography on silica gel (ethyl acetate–ethanol 98:2): $[\alpha]_D^{25}$ −40° (*c* 0.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.82 (s, 3H), 3.42 (s, 3H), 3.60 (dd, 1H, *J* = 5.0), 3.65 (s, 3H), 3.75 (dd, 1H, *J* = 3.8), 4.10 (d, 1H, *J* = 8.8), 4.37 (m, 1H), 4.71 (q, 1H), 6.40 (d, 1H, exchangeable with D_2O), 6.93 (s, 1H), 7.08 (t, 1H, *J* = 7.5), 7.23 (m, 2H), 7.47 (d, 1H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 23.2, 32.9, 44.3, 54.1, 60.0, 71.8, 77.7, 107.6, 109.7, 119.2, 119.7, 122.4, 126.8, 127.8, 137.5, 170.8, 174.6; IR (neat) 1662, 1782, 3388 cm^{-1}; mass spectrum (EI), *m/z* 316 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O_4 \cdot 0.3C_2H_5OH$: C, 63.74; H, 6.64; O, 20.76. Found: C, 64.11; H, 6.98; O, 21.03.

***tert*-Butyldimethylsilyl 2-Acetamido-2,3-dideoxy-3-*C*-[3-(1-methylindolyl)]-5-*O*-methyl-α-(and β)-D-arabinofuranoside (10).** To a solution of aziridine **9** (285 mg, 0.95 mmol) in *N*-methylindole (250 μL, 1 mmol) at 0 °C under nitrogen was added boron trifluoride etherate (122 μL, 2 mmol). The reaction mixture was stirred for 1.5 h at 0 °C and ethyl acetate (50 mL) was added. The solution was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL), the organic phase was dried over Na_2SO_4, and the solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel using ethyl acetate–heptane (1:1) as developer. The β-anomer of **10** (50%) was first eluted followed by the α-anomer (25%). **β-10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.18 (s, 3H), 0.20 (s, 3H), 0.95 (s, 9H), 1.84 (s, 3H), 3.34 (s, 3H), 3.50 (m, 2H, *J* = 7.0), 3.74 (s, 3H), 4.10 (m, 2H), 4.88 (m, 1H), 5.43 (d, 1H, *J* = 4.0), 5.71 (d, 1H, *J* = 9.0, exchangeable with D_2O), 7.08 (s, 1H), 7.11–7.30 (m, 3H), 7.60 (d, 1H, *J* = 8.0); ^{13}C NMR (250 MHz, $CDCl_3$) δ − 5.2, −4.2, 17.9, 23.2, 25.7, 32.6, 39.8, 57.1, 59.0, 74.9, 83.8, 95.8, 109.4, 110.0, 118.6, 119.0, 121.7, 126.5, 127.9, 137.2, 169.7. **α-10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.16 (s, 3H), 0.90 (s, 9H), 1.80 (s, 3H), 3.51 (s, 3H), 3.65 (m, 2H, *J* = 2.0), 3.74 (m, 4H), 4.38 (dt, 1H, *J* = 6.0 and 2.0), 4.60 (dd, 1H, *J* = 3.0 and 8.0), 5.35 (s, 1H), 6.40 (d, 1H, exchangeable with D_2O), 7.08 (s, 1H), 7.20 (m, 4H), 7.60 (d, 1H); IR (neat) 1662, 1782, 3388 cm^{-1}; mass spectrum (EI), *m/z* 432 (M^+). Anal. Calcd for $C_{23}H_{36}N_2O_4Si$: C, 64.77; H, 8.62; N, 6.19. Found: C, 64.96; H, 8.38; N, 6.13.

2-Acetamido-2,3-dideoxy-3-*C*-[3-(1-methylindolyl)]-5-*O*-methyl-α,β-D-arabinofuranose (11). A solution of compound **10** (53 mg, 0.13 mmol) (α,β mixture) in THF (10 mL) was treated at 0 °C with a solution of 1 M tetrabutylammonium fluoride in THF (0.204 mL, 0.2 mmol) for 30 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative chromatography on silica gel (ethyl acetate–methanol, 95:5) yielding **11** as a mixture of anomers (39 mg, 98%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.80 (s, 1.8 H), 1.85 (s, 1.2 H), 3.00 (bs, 1H, exchangeable with D_2O), 3.22 (s, 1.2 H), 3.25 (s, 1.8 H), 3.40 (m, 3H, *J* = 3.0), 3.66 (s, 3H), 4.15 (dt, 0.6 H, *J* = 7.0 and 3.0), 4.40 (m, 0.4 H), 4.70 (m, 1H), 5.27 (dd, 1H, *J* = 4.0 and 2.0), 7.00 (t, 1H), 7.10 (m, 3H, partly exchangeable with D_2O), 7.28 (d, 1H), 7.56 (d, 0.6 H), 7.70 (d, 0.4 H). This sensitive material was used in the next step without further purification.

2-Acetamido-2,3-dideoxy-3-*C*-[3-(1-methylindolyl)]-5-*O*-methyl-D-arabinonolactone (12). To a solution of **11** (α,β-mixture; 78 mg, 0.22 mmol) in acetonitrile (5 mL) held at 0 °C was added freshly activated, powdered 4-Å molecular sieve (100 mg), 4-methylmorpholine *N*-oxide (44 mg, 0.38 mmol), and tetrapropylammonium perruthenate (10 mg, 0.03 mmol). After 1 h, the mixture was diluted with ethyl acetate (30 mL) and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by preparative chromatography on silica gel (ethyl acetate-heptane 1:1), yielding compound **12** as a white solid (44 mg, 62%): mp 87–90 °C; $[\alpha]_D^{25}$ − 54.8° (*c* 0.83, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.96 (s, 3H), 3.44 (s, 3H), 3.65 (oct, 2H), 3.77 (s, 3H), 3.87 (dd, 1H, *J* = 8.0 and 10.0 Hz), 4.45 (m, 1H), 5.22 (dd, 1H), 6.34 (d, 1H, exchangeable with D_2O), 7.16 (m, 2H), 7.29 (m, 2H), 7.58 (d, 1H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 23.0, 33.0, 40.3, 54.5, 59.5, 70.9, 82.9, 108.6, 109.9, 118.5, 119.8, 122.3, 127.1, 127.6, 137.4, 170.6, 173.7; IR (neat) 1668, 1781, 3296 cm^{-1}; mass spectrum (EI), *m/z* 316 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.55; H, 6.32; O, 20.25. Found: C, 64.59; H, 6.61; O, 20.52.

Methyl 2-Acetamido-5-*O*-benzyl-2,3-dideoxy-3-*C*-[3-(1-methylindolyl)]-β-D-arabinofuranoside (14). To a solution of aziridine **13** (110 mg, 0.4 mmol) in *N*-methylindole (**6**) (105 μL, 0.8 mmol) held at 0 °C under nitrogen was added boron trifluoride etherate (75 μL, 0.6 mmol). After 45 min, ethyl acetate (5 mL) was added to the solidified reaction mixture. The resulting solution was washed successively with saturated aqueous Na_2CO_3 (5 mL) and with water (10 mL). The organic phase was then dried over Na_2SO_4, and the solvents were removed in vacuo.

Purification of the residue by chromatography on silica gel using ethyl acetate as developer yielded compound **14** as a colorless oil (91 mg, 56%). Traces of ethyl acetate were removed by codistillation with CCl_4: $[\alpha]^{25}_D$ − 47.0° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, C_6D_6) δ 1.42 (s, 3H), 2.97 (s, 3H), 3.38 (s, 3H), 3.70 (oct, 2H), 4.00 (dd, 1H, J = 10.0 and 11.6), 4.25 (m, 1H), 4.54 (dd, 2H, J_{gem} = 12.1), 5.00 (d, 1H, J = 4.5), 5.36 (m, 1H), 5.51 (d, 1H, J = 9.5, exchangeable with D_2O), 7.05–7.46 (m, 8H), 7.90 (d, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 23.3, 32.8, 40.1, 54.6, 54.9, 56.1, 71.9, 73.2, 73.4, 84.1, 101.6, 109.5, 109.9, 118.7, 119.1, 121.7, 126.5, 127.5, 127.6, 127.9, 128.3, 137.1, 138.3, 169.9; IR (neat) 1665, 3303 cm^{-1}; mass spectrum (EI), m/z 408 (M^+), 350 (M^+ − NHAc). Anal. Calcd for $C_{24}H_{28}N_2O_4 \cdot 1/4CCl_4$: C, 65.17; H, 6.27; N, 6.27. Found: C, 64.99; H, 6.32; N, 6.19.

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