# STEREOCHEMICAL OBSERVATIONS IN THE SYNTHESIS OF NOVEL 1,4,5,9b-TETRAHYDRO-5-PHENYL-2*H*-AZETO[2,1-*a*]ISO-QUINOLIN-2-ONE DERIVATIVES[1]

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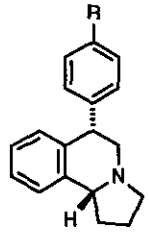
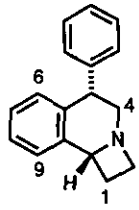
**Abstract** - Imine (**5**) reacted with $Cl_2CHC(O)Cl$ in the presence of $Et_3N$ to give β-lactams (**7a**) and (**7b**) in a 4:1 ratio. The stereochemistry of cycloadduct (**7a**) was confirmed by X-ray analysis. Uncyclized intermediates were identified. Reduction of dichloro β-lactam (**7a**) with Zn/HOAc gave mostly *exo* monochloride (**13a**), with high stereoselectivity (10:1 ratio). Reduction of a mixture of *exo* and *endo* monochlorides (**13a**) and (**13b**) with Zn/HOAc indicated that the more sterically hindered *endo* chlorine is preferentially attacked. Reduction of (**7a**) with $Bu_3SnH$ gave β-lactam (**14a**) as the major product.

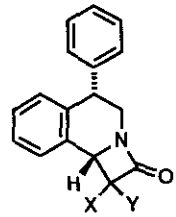
Drugs that interfere with the uptake of serotonin and/or norepinephrine are very important in the treatment of depression.[2] We have described a series of pyrrolo[2,1-*a*]isoquinolines, exemplified by (**1**) and (**2**), with anti-depressant activity and the ability to inhibit uptake of serotonin, norepinephrine, and dopamine into neurons.[3]




**1** R = H
**2** R = SMe




**3**

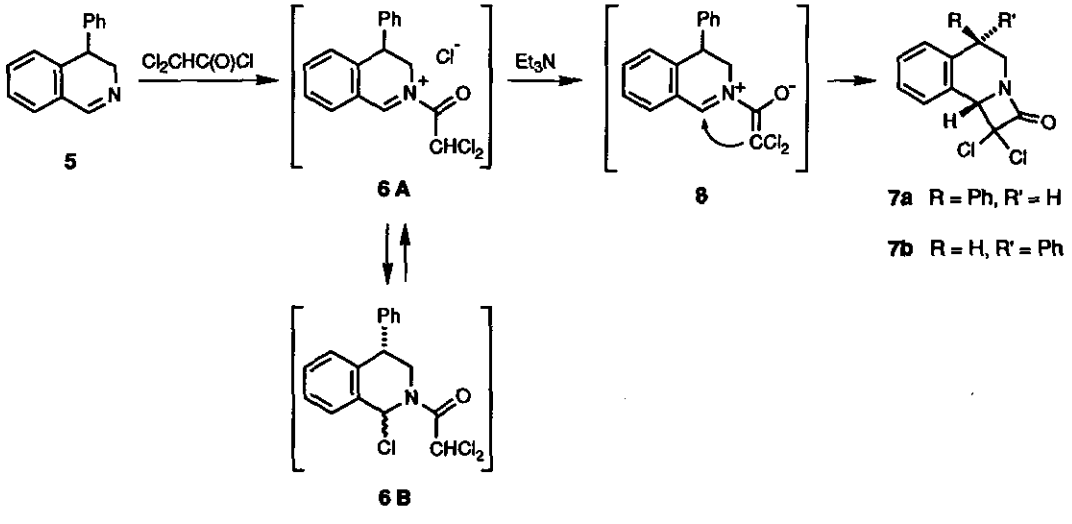



**4**

In the course of our work to define structure-activity relationships, we synthesized the corresponding azetidine analogue (**3**), which has already been reported.[3a] This paper describes the results of an alternative chemical approach to **3** involving β-lactam intermediates [viz. **4** ].

## β-LACTAM FORMATION

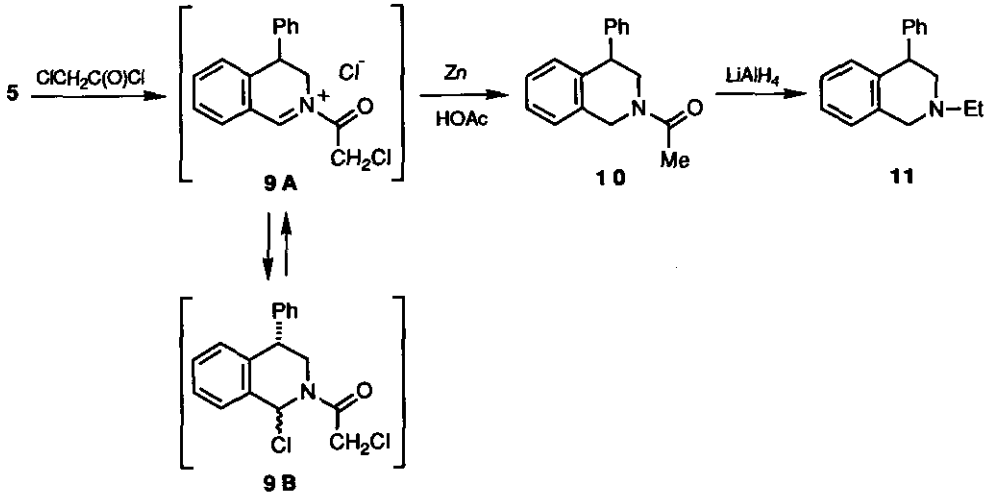
The β-lactam ring system can be effectively produced by the cycloaddition of a reactive ketene species with an imine.[4] This seemed like a convenient method for the case at hand because imine (**5**) is readily available.[5] Imine (**5**) in methylene chloride was treated at -40°C with dichloroacetyl chloride and then triethylamine. After warming the reaction to 23°C, washing with water, and evaporating to dryness, no cyclized product (**7**) was detected. The isolated crude product was unstable and contained several components ($^1$H nmr; tlc), which are supposedly related to intermediate (**6**). Although the $^1$H nmr spectrum showed no iminium proton for **6A** , it was reasonably consistent with a diastereomeric mixture of **6B** , or a congener thereof with the labile chlorine replaced by hydroxy. The same reaction conducted in toluene at reflux, again by adding the triethylamine last,




afforded the desired dichloro β-lactam products (**7a**) and (**7b**), in a ratio of 4:1 (51% isolated yield). When **5** and dichloroacetyl chloride were heated in toluene without triethylamine for 20 min, followed by concentration to dryness, an uncyclized intermediate was obtained instead. The $^1$H nmr spectrum of this material suggested a

mixture of **6A** and **6B** enriched in the latter. Consequently, the cycloaddition process to **7** appears to proceed in a stepwise fashion. The 1,4 diastereoselectivity would be determined when intermediate (**6**) cyclizes, via zwitterion (**8**), perhaps because the phenyl substituent prefers a pseudoequatorial orientation, and the enolate carbon prefers to approach from an equatorial direction. A sense of this conformational arrangement can be gleaned from examining the conformation shown by the X-ray structure of **7a** in Figure 1.

The reaction of imine (**5**) with chloroacetyl chloride and triethylamine at -40°C furnished an analogous uncyclized intermediate. Again, the $^1$H nmr spectrum did not show an iminium proton, for (**9A**), but it was reasonably consistent with a diastereomeric mixture of **9B** , or a congener thereof with the labile chlorine replaced by hydroxy. In this case, the composition of **9** (or its hydroxy covalent addition species) was verified by reduction with zinc and acetic acid to acetamide (**10**), which was further transformed with $LiAlH_4$ to known (**11**).[3a] When **5** and chloroacetyl chloride were heated in toluene without triethylamine, followed by concentration to dryness, an uncyclized intermediate was obtained, the $^1$H nmr spectrum of which suggests a mixture of **9A** and **9B** enriched in the latter.




The production of intermediate adducts, such as **6** and **9** , is anticipated from literature precedent.[4] Although this type of reaction can well proceed by a nonconcerted ketene cycloaddition,[4b] there are cases that involve acyclic adducts from imine acylation (*N*-acyliminium ions), and this pathway is favored by the mode of addition

employed here (amine added to already combined acid halide and imine).[4c-4h]

The structure and stereochemistry of **7a** was confirmed by single-crystal X-ray analysis. There were eight molecules per unit cell and two types of crystallographically independent molecules, which differed by minor changes in conformation. One of the molecules is depicted in Figure 1. The nitrogen atom of the β-lactam ring is moderately pyramidal in both forms, as $C_4$ is 0.44/0.48 Å displaced from the plane defined by the four atoms of the 4-membered ring ($C_1$-$C_2$-$N_3$-$C_{9b}$); also, nitrogen $N_3$ is 0.26 Å above the plane generated by atoms $C_2$,

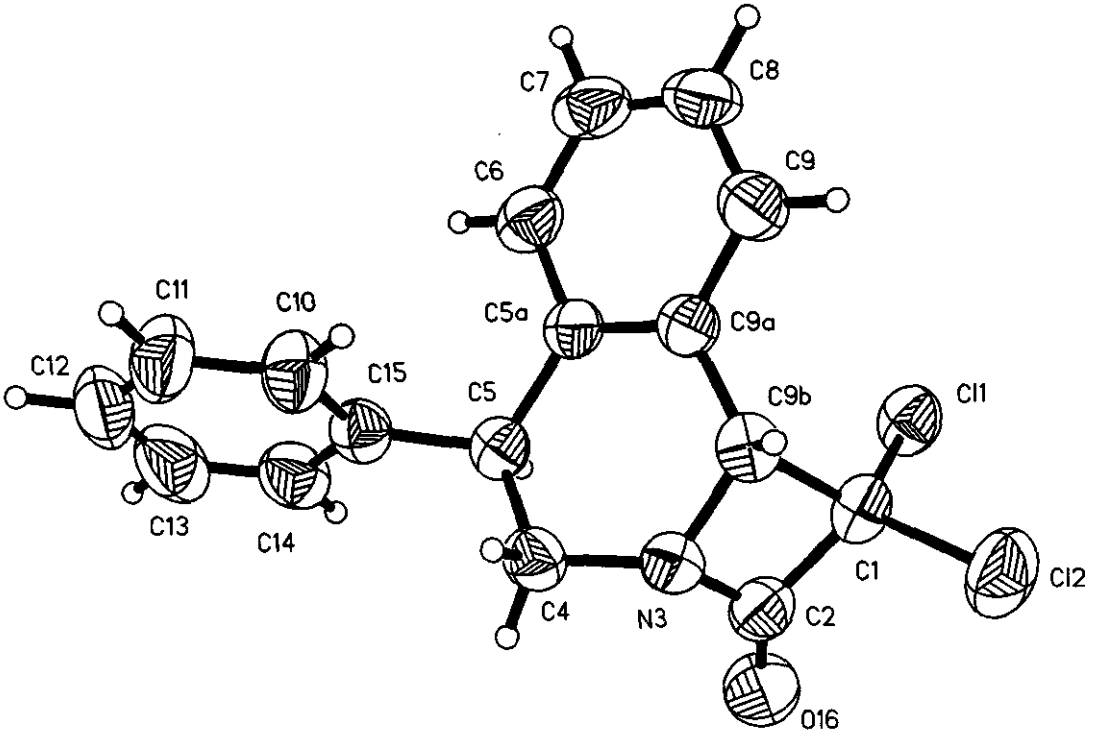



**Figure 1.** Perspective drawing of one of the two crystallographically independent molecules (molecule A), showing the atom-numbering scheme. All nonhydrogen atoms are represented by thermal vibration ellipsoids encompassing 50% of their electron density; hydrogen atoms are represented by arbitrarily small spheres.

$C_4$, and $C_{9b}$. The cis-fused β-lactam ring causes the adjacent 6-membered ring to adopt an envelope conformation, rather than a half-chair conformation. This arrangement is characterized by the virtual coplanarity of atoms $N_3$, $C_5$, $C_{5a}$, $C_{9a}$, and $C_{9b}$. The 5-phenyl group adopts an equatorial orientation, but $C_1$ of the β-lactam is bent inward from a normal equatorial orientation such that this end of the molecule is puckered and $H_{9b}$ is disposed halfway between an axial and equatorial position ($\angle H_{9b}$-$C_{9b}$-$C_{9a}$-$C_9$ = 53.2°). Thus, one of the chlorine atoms, namely $Cl_1$, is placed in an *endo* environment that is more sterically encumbered.

Reaction of imine (**5**) with dibromoacetyl bromide and triethylamine in refluxing benzene (too much decomposition occurred in refluxing toluene) produced dibromo β-lactams (**12a**) and (**12b**) in a ratio of 86:14, which is close to the 4:1 ratio for the corresponding dichloro reaction. However, this reaction was comparatively poor in that multiple by-products were formed and the isolated yield of **12a** was only 10%. Also, the thermal instability of these β-lactams was evidenced by their apparent reversion to imine (**5**) on glc analysis. Use of dibromoacetyl chloride was problematic in this cycloaddition because a more complex product mixture was obtained by virtue of halogen exchange.

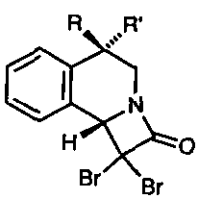
## DEHALOGENATION CHEMISTRY

We wanted to remove both chlorine atoms present in **7a** by reduction with zinc in acetic acid;[6] however, treatment at 75°C for 3 h gave mostly monochloro lactam (**13a**), along with **13b** and **14a** in minor quantities [ **13a** / **13b** = 10:1]. Unfortunately, prolonged heating caused extensive decomposition. The trans stereochemistry of the β-lactam ring of **13a** was established by 300-MHz $^1$H nmr via the vicinal H-H coupling, $^3J(1,9b)$ = 1.6 Hz; also, a significant NOE was observed between $H_1$ and $H_{9b}$ in **13b** , but not in **13a** . To explain this stereoselectivity, we suggest the formation of an intermediate chlorozinc enolate, which is inert to further reaction as such. The enolate is then protonated from the more hindered *endo* face (qv. X-ray discussion above) to give the observed major product (**13a**), which is much less reactive to Zn/HOAc, as demonstrated below.

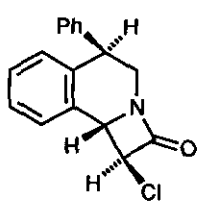
Reaction of **7a** with $Bu_3SnH$ in toluene at 110°C was time-dependent. When the reaction was refluxed 1 h, diastereomeric monochlorides (**13a**) and (**13b**) were the major products (in a ratio of 1:1);[7] whereas, prolonged

heating for about 24 h afforded mainly **14a** . This conversion of **7a** to **14a** was accomplished rather cleanly. On exposure of a 1:1 mixture of **13a** and **13b** to Zn/HOAc, only chloro lactam (**13b**) was readily consumed; **13a** was virtually untouched. Thus, the more sterically hindered *endo* chlorine is preferentially removed in this Zn/HOAc process. This point could not be determined in the reduction of **7a** to **13a / 13b** , although one might now speculate that the more sterically hindered chlorine in **7a** is also removed preferentially. This result supports our proposal that the relative unreactivity of the major monochloro product, (**13a**), was responsible for the 10:1 product distribution. Indeed, since the reactive isomer (**13b**) is just a minor product in the reaction of **7a** with Zn/HOAc, the sluggishness of bis-dechlorination can be appreciated: material with an *endo* chlorine is not available for reduction.

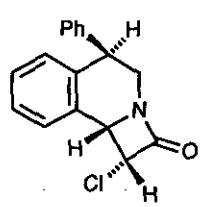
Debromination of **12a** with $Bu_3SnH$ at 23°C proceeded cleanly to give a good yield of **14a** . The monobromo intermediates were not present to any significant extent during the course of the reaction. However, treatment of **12a** with Zn/HOAc at 23°C, resulted in considerable decomposition and only a low yield (15%) of **14a** was isolated.



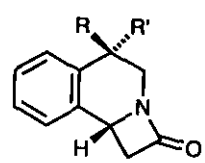

**12a** R = Ph, R' = H
**12b** R = H, R' = Ph




**13a**




**13b**

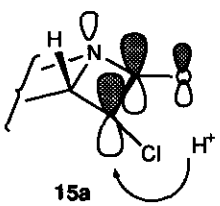



**14a** R = Ph, R' = H
**14b** R = H, R' = Ph

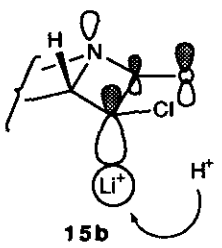
Stereoselective removal of one of two halogens on a ring-fused β-lactam has already been reported.[6-9] Three different reduction systems, including Zn/HOAc and tin hydride, have been used.[6-8] For our case, the Zn/HOAc reduction was more stereoselective than the tin hydride reduction. In the reported Zn/HOAc reduction of a dibromopenicillanate, the trans monobromide was preferentially produced, wherein an intermediate zinc enolate was protonated from the more sterically hindered *endo* face,[6] in analogy to our case. A similar steric bias (10:1) was reported for Rh(I)-mediated monodehalogenation in a protic solvent.[8a] Metal complexation effects have been proposed[8,9] or implied[6] to rationalize such unexpectedly favored stereochemistry for halogen replacement. Our system has no convenient heteroatom for metal complexation or for guiding addition.

Therefore, to rationalize the observed reactivity pattern, which runs counter to steric factors, it is necessary to analyze electronic factors.

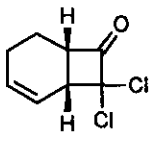
For the chemistry of **7a** , one might suggest that there is a favored alignment of electron density on the α-carbon orthogonal to the carbonyl, both in dehalogenation to give enolate and in protonation of enolate. However, both chlorine atoms in **7a** are equivalently disposed relative to the carbonyl from a torsional angle standpoint; the same holds true for both faces of the enolate. The key component here must be the lone electron pair on the bridgehead nitrogen, which is oriented on the *exo* face and cannot conjugate effectively with the carbonyl because of the geometric constraints of the β-lactam ring. Thus, the nitrogen would have mostly $sp^3$ character, as can appreciated by its pyramidalization in the X-ray structure of **7a** . The electron density of the enolate would be concentrated on the α-carbon ($C_1$). AM-1 calculations of the HOMO for this enolate, with an energy-minimized geometry, support strong electron density between the two carbons ($C_1$ and $C_2$) and low electron density between $C_2$ and $O_2$ [qv. **15a** ]. The enolate has charge distributed about equally on $O_2$ and $C_1$.[10] It is conceivable that the directed nitrogen lone pair on the *exo* side of the molecule may exert a strong electronic repulsion to attack of a proton from the face of the β-lactam *syn* to it. However, a MNDO (MOPAC) calculation on the lithium enolate affords a more convincing explanation. The most stable HOMO shows the lithium ion attached to the *endo* face of the enolate with significant pyramidalization at $C_1$ (significant $sp^3$ character), with the directed nitrogen lone pair on the *exo* face of the 4-membered ring apparently exerting a strong repulsion vis-a-vis the electron density at $C_1$, such that an *anti* disposition is preferred [qv. **15b** ].[11] That is, the proton favors an approach *anti* to the nitrogen lone pair, in a fully-formed or incipient enolate. In this respect, it is interesting that Zn/HOAc monodehalogenation of dichloro ketone (**16**) proceeds with the *opposite* stereochemistry, in a 17:1 cis/trans ratio.[12]



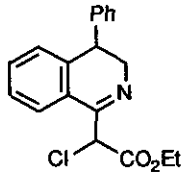

**15a**



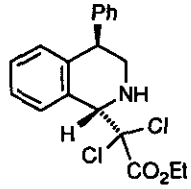

**15b**




**16**




**17**




**18**

## β-LACTAM CLEAVAGE

Treatment of **7a** with ethanolic HCl yielded an unstable species (**17**), instead of ester (**18**). Attempted $LiAlH_4$ reduction of **7a** gave a mixture of unidentified products instead of the desired azetidine derivative (**3**).

## EXPERIMENTAL SECTION

**General Methods.** The X-ray crystallography work on **7a** was conducted by Crystalytics Co., Lincoln, Nebraska, USA. All melting points are corrected by calibration to a set of reference standards. $^1H$ Nmr spectra were obtained on a Bruker AFC 300-WB (300 MHz), a Varian EM-390 (90 MHz), or a Bruker AM-400 (400 MHz) spectrometer in $CDCl_3$ (unless otherwise denoted) with $Me_4Si$ as an internal reference (nmr abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). $^{13}C$ Nmr spectra were obtained at 100.6 MHz on the Bruker AM-400 in $CDCl_3$. Infrared spectra (KBr) were recorded on a Nicolet SX 60 FT spectrometer. Chemical-ionization mass spectra (CI-ms) were recorded on a Finnigan 3300 system with $CH_4$ as the reagent gas. Data from glc/ms were recorded by using a Hewlett-Packard 5890/5920 system. Fast-atom-bombardment mass spectra (FAB-ms) were recorded on a VG 7070E high resolution mass spectrometer by using an argon beam at 7 kV and 2 mA of current in a thioglycerol matrix. Where necessary, analytical samples were obtained by preparative tlc on tapered silica gel plates (300-1700 mm). Preparative hplc separations were performed on a Waters Prep 500A instrument. Tlc analyses were performed on Whatman 250-μm silica gel plates with visualization by uv fluorescence and iodine staining. Glc analyses were performed on a Hewlett-Packard 5890 gas chromatograph with a Chrompack CP SIL 5 CB capillary column (25 m x 0.25 mm).

**Reaction of (5) with Dichloroacetyl Chloride. Preparation of (7).** A mixture of **5** (2.00 g, 9.6 mmol) and dichloroacetyl chloride (1.51 g, 10 mmol) in toluene (26 ml) was heated to reflux under argon. After 20 min, triethylamine (1.09 g, 10 mmol) in toluene (26 ml) was added. The reaction mixture was refluxed for 60 min, stirred at 23°C for 18 h, and filtered. The filtrate was concentrated under reduced pressure to give a crude syrup (3.7 g), which was chromatographed (preparative hplc; hexane/ethyl acetate, 4:1) to give **7a** and **7b** in a ratio of 4:1 [1.23 g of **7a**, and 0.32 g of **7b**; 51%]. Compound (**7a**) was recrystallized from ethyl acetate/hexane to give white needles: mp 140-141°C; ir (KBr) $\nu_{max}$ (C=O) 1782 $cm^{-1}$; $^1H$ nmr (300

MHz) δ 3.15 (dd, 1H, J = 12.9, 15.3 Hz, $H_4$), 4.17-4.25 (m, 2H, $H_4$ and $H_5$), 5.21 (s, 1H, $H_{9b}$), 6.81 (d, 1H, J = 7.9 Hz, $H_6$), 7.10-7.45 (m, 8H, arom.); CI-ms: m/z 319 (M+1). Anal. Calcd for $C_{17}H_{13}NOCl_2$: C, 64.17; H, 4.12; N, 4.40; Cl, 22.28. Found: C, 63.83; H, 4.13; N, 4.25; Cl, 22.04. Compound (**7b**): mp 58-60°C; ir (KBr) $\nu_{max}$ (C=O) 1782 $cm^{-1}$; $^1H$ nmr (300 MHz) δ 3.62 (dd, 1H, J = 5.5, 13.8 Hz, $H_4$), 4.15 (dd, 1H, J = 9.5, 13.8 Hz, $H_4$), 4.24 (dd, 1H, J = 5.5, 9.5 Hz, $H_5$), 5.1 (s, 1H, $H_{9b}$), 6.97 (m, 1H, $H_6$), 7.10-7.45 (m, 8H, arom.); CI-ms: m/z 319 (M+1). Anal. Calcd for $C_{17}H_{13}NOCl_2 \cdot 0.2\ H_2O$: C, 63.45; H, 4.20; N, 4.35; $H_2O$, 1.12. Found: C, 63.40; H, 4.35; N, 4.27; $H_2O$, 0.75.

**Conversion of 5 to 10 .** A mixture of imine (**5**) (2.0 g, 9.8 mmol) in $CH_2Cl_2$ (20 ml) was cooled (-40 °C) and treated dropwise with a mixture of chloroacetyl chloride (1.17 g, 10 mmol) in $CH_2Cl_2$ (5.0 ml), followed by the addition of a mixture of triethylamine (0.99 g, 10 mmol) in $CH_2Cl_2$ (5.0 ml). After stirring for 30 min, the mixture was allowed to stir at 23°C overnight and filtered. The filtrate was washed (water, satd. $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated under reduced pressure to 2.35 g of a crude yellow solid, whose $^1H$ nmr spectrum was consistent with a reaction "intermediate related to **9B** ". As a follow-up to this, a mixture of (**5**) (0.25 g, 1.2 mmol), and chloroacetyl chloride (0.15 g, 1.2 mmol) in toluene (10 ml) was refluxed for 20 min. The reaction mixture was cooled and concentrated under reduced pressure to give a crude yellow solid (0.37 g, 96%), containing a mixture of **9A** and **9B** , enriched in **9B** . $^1H$ Nmr (300 MHz) δ 3.21-4.49 (m, 4H), 4.51 [s, 2H, $CH_2Cl$ of **9B** ], 6.74-7.68 (m, arom.), 7.75 [dd, 1H, J = 7.1, 7.7 Hz, $H_7$ of **9A** ], 7.95 [d, 1H, J = 7.4, $H_8$ of **9A** ], 9.03 [s, 1H, $H_1$ of **9A** ]. A mixture of "intermediate related to **9B** " (2.0 g, 7.1 mmol) in acetic acid (30 ml) was stirred at 70°C, zinc (0.8 g) was added, and the mixture was stirred at that temperature for 45 min. It was cooled, filtered, and concentrated under reduced pressure to a foam, which was dissolved in $CH_2Cl_2$. The organic solution was washed (water, satd. $NaHCO_3$), dried ($K_2CO_3$), and concentrated under reduced pressure to a semisolid (1.5 g). A sample was chromatographed (preparative tlc; hexane/ethyl acetate, 1:1) to give a semisolid, **10** . $^1H$ Nmr (300 MHz) δ 1.74 (s, 3H, $CH_3$), 3.87 (d, 2H, J = 4.4 Hz, $H_3$), 4.29 (d, 1H, J = 4.4 Hz, $H_4$), 4.57 (d, 1H, J = 17.4 Hz, $H_1$), 5.29 (d, 1H, J = 17.4 Hz, $H_1$), 6.93-7.44 (m, 9H, arom.); CI-ms: m/z 252 (M+1).

**Conversion of 10 to 11 .** Crude **10** (0.1 g, 0.4 mmol) in anhydrous ether (1.0 ml) was treated with $LiAlH_4$ (0.03 g, 0.8 mmol), and stirred under argon for 3 h. The mixture was treated with $H_2O$ (0.2 ml), 15%

NaOH (0.4 ml) and $H_2O$ (0.4 ml), stirred for 15 min, and filtered. The organic extract was washed (1 N NaOH, water), dried ($K_2CO_3$), and concentrated under reduced pressure to a syrup **11** [3a] (0.05 g, 26% yield). $^1H$ Nmr (90 MHz) δ 1.05-1.29 (t, 3H), 2.36-2.68 (m, 3H, $CH_2$, $H_3$), 2.96-3.22 (dd, 1H, J = 6.6, 13.3 Hz, $H_3$), 3.44-3.95 (dd, 1H, J = 9.9, 14.0 Hz, $H_1$), 4.35-4.86 (m, 1H, $H_4$), 6.68-7.35 (m, 9H, arom.).

**Preparation of Dibromoacetyl Bromide.** Dibromoacetic acid (10.9 g, 0.05 mol) and phosphorus tribromide (13.5 g, 0.05 mol) were combined and stirred at 23°C; bromine (8.0 g, 0.05 mol) was added slowly under an argon atmosphere. After complete addition, the reaction was heated at 90°C for 1.75 h, and then cooled to 10°C. The crude product was distilled to afford dibromoacetyl bromide (13.86 g, 49%): $bp_4$ 57-61°C; $^1H$ nmr (300 MHz) δ 6.11 (s); $^{13}C$ nmr (100.6 MHz) δ 43.6, 158.8.

**Reaction of 5 with Dibromoacetyl Bromide. Preparation of 12 .** Imine (**5**) (2.07 g, 10 mmol) and dibromoacetyl bromide (3.09 g, 11 mmol) were combined in dry benzene (30 ml) under argon and brought to reflux. Triethylamine (1.21 g, 12 mmol) was added dropwise and the reaction was refluxed for 70 min. After cooling to 23°C, the solid was collected by filtration and the filtrate was concentrated to furnish crude product (3.23 g, 79%), which contained **12a** and **12b** in a 86:14 ratio [$^1H$ nmr for $H_{9b}$ δ 5.33 [0.86H, **12a** ] and 5.20 [0.14H, **12b** ]; glc/ms gave $M^+ = 407$ for both **12a** and **12b** . This material was purified by using preparative hplc (hexane/ethyl acetate, 12:1) to give 0.42 g (10%) of **12a** , a sample of which was recrystallized from ethyl acetate/hexane to give pure white crystals, mp 141-142.5°C; ir $\nu_{max}$ (C=O) 1778 $cm^{-1}$; $^1H$ nmr (300 MHz) δ 3.13 (dd, 1H, J = 12.9, 15.2 Hz, $H_{4a}$), 4.15-4.25 (m, 2H, $H_{4e}$ and $H_5$), 5.33 (s, 1H, $H_{9b}$), 6.81 (d, 1H, J = 7.9 Hz, $H_6$), 7.15-7.45 (m, 8H, arom.). Anal. Calcd for $C_{17}H_{13}NOBr_2$: C, 50.16; H, 3.22; N, 3.44. Found: C, 49.95; H, 3.20; N, 3.39.

**Reaction of 7a with Tributyltin Hydride** A mixture of **7a** (0.40 g, 1.2 mmol) and tributyltin hydride (2 ml, 7.5 mmol) in toluene (40 ml) was refluxed for 24 h. After cooling, the reaction mixture was concentrated under reduced pressure give to a syrup, which was dissolved into $CH_2Cl_2$, and washed once with 1 N HCl. The organic extract was concentrated to a syrup, which was washed twice with hexane/acetonitrile (1:1). The extract was concentrated under reduced pressure to give a pale yellow syrup (0.39 g), which was analyzed by glc to consist of **13a** , **13b** , and **14a** , in a ratio of 4:10:86. The crude syrup was chromatographed (preparative tlc; hexane/ethyl acetate, 4:1) to give **13a** as a syrup (0.026 g, 7.5%), **13b** as a white

solid (0.028 g, 8%), and **14a** as a white solid (0.16 g, 55%). The two solids were recrystallized from ethyl acetate/hexane to give fluffy crystals. Compound (**13a**): Anal. Calcd for $C_{17}H_{14}NOCl$: C, 71.96; H, 4.97; N, 4.94. Found: C, 71.39; H, 5.41; N, 4.86. Ir (KBr) $\nu_{max}$ (C=O) 1766 $cm^{-1}$; CI-ms: m/z 284 (M+1); $^1H$ nmr (300 MHz) δ 3.22 (dd, 1H, J = 9.9, 13.2 Hz, $H_4$), 4.17-4.32 (m, 2H, $H_4$ and $H_5$), 4.65 (d, 1H, J = 1.7 Hz, $H_1$), 4.80 (narrow m, 1H, $H_{9b}$), 6.87 (d, 1H, J = 7.9 Hz, $H_6$), 7.14-7.39 (m, 8H, arom.). Compound (**13b**): Anal. Calcd for $C_{17}H_{14}NOCl \cdot 0.2\ H_2O$: C, 71.06; H, 5.05; N, 4.87. Found: C, 70.98; H, 4.62; N, 4.64. mp 191-193°C; ir (KBr) $\nu_{max}$ (C=O) 1761 $cm^{-1}$; CI-ms: m/z 284 (M+1); $^1H$ nmr (300 MHz) δ 3.12 (dd, 1H, J = 10.9, 13.3 Hz, $H_4$), 4.17-4.32 (m, 2H, $H_4$ and $H_5$), 5.01 (d, 1H, J = 4.6 Hz, $H_1$), 5.25 (d, 1H, J = 4.6 Hz, $H_{9b}$), 6.82 (d, 1H, J = 7.9 Hz, $H_6$), 7.13-7.39 (m, 8H, arom.). Compound (**14a**): Anal. Calcd for $C_{17}H_{15}NO \cdot 0.1\ H_2O$: C, 81.90; H, 6.05; N, 5.62. Found: C, 81.31; H, 6.10; N, 5.58. mp 136-138°C, ir (KBr) $\nu_{max}$ (C=O) 1748 $cm^{-1}$; CI-ms: m/z 250 (M+1); $^1H$ nmr δ 2.85 (dd, 1H, J = 2.2, 14.8 Hz, $H_1$), 3.16 (dd, 1H, J = 9.7, 13.5 Hz, $H_4$), 3.56 (dd, 1H, J = 5.2, 14.8 Hz, $H_1$), 4.15 (dd, 1H, J = 6.6, 13.5 Hz, $H_4$), 4.45 (dd, 1H, J = 6.6, 9.7 Hz, $H_5$), 4.70 (m, $H_{9b}$), 6.85 (d, 1H, J = 7.8 Hz, $H_6$), 7.12-7.38 (m, 8H, arom.).

**Reaction of 7a with Zinc and Acetic Acid.** A mixture of **7a** (0.10 g, 0.31 mmol) and zinc dust (0.20 g) in glacial acetic acid (2.5 ml) was stirred at 75°C for 3 h. After cooling, the reaction mixture was treated with water and extracted twice with $CH_2Cl_2$. The extract was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to a light brown syrup (0.03 g, 34%) which was analyzed by glc to consist of **13a** , **13b** , and **14a** in a ratio of 73:7:20. $^1H$ Nmr of the crude mixture confirmed this ratio.

**Reaction of 13 with Zinc and Acetic Acid.** A mixture of a 1:1 ratio of **13a** and **13b** (8.0 mg, 0.028 mmol), zinc dust (2.0 mg) in glacial acetic acid (2.0 ml) was stirred at 75°C for 4 h. After cooling, the reaction mixture was treated with water and extracted twice with $CH_2Cl_2$. The organic extract was dried ($MgSO_4$), and concentrated to a brown syrup (3.0 mg, 35%) which was analyzed by glc to consist of only **13a** . $^1H$ Nmr of this crude mixture confirmed this structure. The aqueous extract was also concentrated under reduced pressure to give a semi-solid (2.0 mg) which contained only inorganic material [no **14a** by tlc].

**Reduction of 12a with Tributyltin Hydride.** Tributyltin hydride (175 mg, 0.60 mmol) was added to dibromo lactam (**12a**) (41 mg, 0.10 mmol) in benzene (3 ml) and stirred at 23°C for 3 h. 1 N HCl (5 ml) was

added; the mixture was stirred for 30 min; the organic layer was separated and evaporated in vacuo to an oil. The crude product was purified by preparative tlc to afford white solid **14a** (15.8 mg, 63%). $^1$H Nmr (300 MHz) δ 2.85 (dd, 1H, J = 2.2, 14.8 Hz, $H_{1a}$), 3.16 (ddd, 1H, J = 0.7, 9.7, 13.3 Hz, $H_{4a}$), 3.56 (dd, 1H, J = 5.1, 14.9 Hz, $H_{1e}$), 4.16 (dd, 1H, J = 6.6, 13.3 Hz, $H_{4e}$), 4.33 (dd, 1H, J = 6.6, 9.7 Hz, $H_5$), 4.70 (m, $H_{9b}$), 6.87 (d, 1H, J = 7.8 Hz, $H_6$), 7.1-7.4 (m, 8H, arom.).

**Reaction of 7a with Ethanolic HCl.** A mixture of **7a** (0.15 g, 52 mmol) in 3% ethanolic HCl (20 ml) was refluxed for 4 h, concentrated under reduced pressure to an oil, which was dissolved in $CH_2Cl_2$, washed with 3 N NaOH, dried ($K_2CO_3$), concentrated to a light yellow syrup, and chromatographed (preparative tlc; hexane/ethyl acetate, 4:1) to give **17** as a syrup (0.02 g, 12%). $^1$H Nmr (300 MHz) δ 1.39 (t, 3H, J = 6.6 Hz, $CH_3$), 3.65 (m, 2H, $CH_2$), 3.70 (s, 1H, CHCl), 4.15 (t, 1H, J = 6.6 Hz, $H_3$), 4.21-4.48 (m, 2H, $H_4$ and $H_3$), 6.98 (d, 1H, J = 7.8 Hz, $H_6$), 7.09-7.46 (m, 8H, arom.); CI-ms: m/z 328 (M+1).

**Generation of 6 and Its Bromo Congener.** A mixture of **5** (2.16 g, 10 mmol) and $CH_2Cl_2$ (30 ml) was cooled to -40°C and treated dropwise with a solution of dichloroacetyl chloride (1.60 g, 10 mmol) in $CH_2Cl_2$ (5 ml), followed by the addition of triethylamine (1.21 g, 10 mmol) in $CH_2Cl_2$ (5 ml). After stirring for 30 min, the mixture was allowed to stir at 23°C overnight and filtered. The filtrate was washed (water, satd. $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated to 2.78 g of a crude brown solid, the $^1$H nmr (300 MHz) of which was consistent with a reaction intermediate. As a follow-up, a mixture of **5** (0.25 g, 1.2 mmol) and dichloroacetyl chloride (0.19 g, 1.2 mmol) in toluene (10 ml) was refluxed for 20 min, cooled, and concentrated under reduced pressure to a crude yellow solid (0.46 g), a mixture of **6A** and **6B** that was enriched in **6B**. $^1$H Nmr (300 MHz) δ 3.96-4.54 (m, 3H), 5.35 [s, 1H, $H_1$ in **6B**], 6.15 (s, 1H, $CHCl_2$ in **6A**), 6.26 [s, 1H, $CHCl_2$ in **6B**], 6.67-7.68 (m, arom.), 7.75 [dd, 1H, J = 7.1, 7.7 Hz, $H_7$ in **6A**], 7.95 [d, 1H, J = 7.4 Hz, $H_8$ in **6A**], 9.03 [s, 1H, $H_1$ in **6A**]. A mixture of **5** (69 mg, 0.33 mmol) and dibromoacetyl chloride (79 mg, 0.33 mmol) in toluene (1 ml) was refluxed for 15 min, cooled, and evaporated in vacuo to give an oily product containing one major component, identified as the dibromo congener of **6A** : $^1$H nmr (400 MHz) δ 4.18 (m, 1H, $H_{3a}$), 4.35 (dd, 1H, J = 7.2, 15.8 Hz, $H_{3e}$), 4.58 (dd, 1H, J = 7.2, 11.3 Hz, $H_4$), 5.83 (s, 1H, $CHBr_2$), 7.1-7.6 (m, arom.), 7.75 (dd, 1H, J = 7.6, 7.8 Hz, $H_7$), 7.95 (d, 1H, J = 7.4 Hz, $H_8$), 9.28 (s, 1H, $H_1$); signals attributable to a minor amount of covalent adducts were also evident.

**X-Ray Crystallography of 7a .** Crystals of **7a** ($C_{17}H_{13}NOCl_2$, mw 318.2, colorless irregular prisms from chloroform/hexanes, 1:3) are monoclinic (space group $P2_1/c$) with $a$ = 16.438(2) Å, $b$ = 10.560(1) Å, $c$ = 18.004(3) Å, $\alpha$ = 90.0°, $\beta$ = 100.63(1)°, $\gamma$ = 90.0°, $V$ = 3071.5(7) Å$^3$, and $d_{calcd}$ = 1.376 g cm$^{-1}$ for $Z$ = 8. The intensity data were collected from a single crystal on a computer-controlled Four-Circle Nicolet Auto-diffractometer with the $\theta$-2$\theta$ scan technique at 293 K in three shells with scattering angles ranging from 3.0° < 2$\theta$ < 125.2° by using Cu K$\alpha$ radiation ($\lambda$ = 1.54184 Å; nickel filter). Of a total of 4909 independent reflections collected, 3804 intensities greater than 3.0$\sigma$($I$) were used. The structure was solved by direct methods by using the *SHELXTL* program, locating the 42 nonhydrogen atoms. Standard Lorentz and polarization corrections were applied to the data; the hydrogen atom positions were located. Structural refinement was accomplished by full-matrix least-squares methods with an anomalous dispersion correction for the chlorine atoms. For molecules A and B, hydrogen atom $H_{9b}$ was located from a difference Fourier synthesis and refined as independent isotropic atoms. The remaining hydrogen atoms were included in the structure factor calculations as idealized atoms. The final discrepancy factors were $R_1$ = 0.046 and $R_2$ = 0.052.

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