mL). Na_2CO_3 was added until the solution pH was about 5. TiO_2 (anatase, MCB, 3.0 g) was added. While being stirred in a quartz tube, the mixture was irradiated with a 500-W Xenon lamp for 10 h. The mixture was centrifuged to isolate the solid, which was then washed 4 times with 25 mL of H_2O. The platinized (grey) TiO_2 was dried in an oven (132 °C) overnight. Lower loading levels were attained by a modification of the same procedure.

Photolysis Procedure. TiO_2 (5 mg) was added to a solution of diacid (0.01 M) in 50 mL of aqueous HNO_3 (pH = 1), which was agitated in an ultrasonic bath for 15 min to form a suspension. Magnetically stirred reaction mixtures in Pyrex tubes were irradiated in a Rayonet photochemical reactor (temperature ca. 52 °C) with 350-nm light for 24 h (unless otherwise noted). The reaction mixtures were filtered through a fritted glass filter before being analyzed by GC or HPLC. Products were identified by comparing retention times and fragmentation patterns obtained by GC/MS with authentic samples. Product yields were determined by GC using 2,4,6-trimethylphenol as an internal standard. The diacids were quantified by HPLC (after neutralization of reaction mixture) with a reverse-phase column. Experiments with *trans*-4-phenyl-*cis*-1,2-cyclohexanedicarboxylic acid (prepared via a Friedel-Crafts arylation of *cis*-1,2,3,6-tetrahydrophthalic acid[34,35]) were performed in 5% H_2O/CH_3CN (because of insolubility in H_2O) and the irradiations were carried out for 72 to 144 h, but were otherwise analogous to the reactions of unsubstituted cyclohexanedicarboxylic acids.

CO_2 Trapping Experiments. CO_2 trapping experiments were run by bubbling gas (N_2, air, or O_2) through the reaction mixture during the irradiation. The effluent gas was then passed through a $Ba(OH)_2$ trap, trapping CO_2 as $BaCO_3$ (measured by weight).[8,18d] Barium hydroxide traps were prepared with saturated $Ba(OH)_2$ in 1 M NaOH. The absence of CO_2 in the purging gas stream was ensured by inserting a $Ba(OH)_2$ trap in the line before the purge gas entered the reaction mixture.

Controls were performed by excluding, respectively, light, catalyst, and diacid to verify that no reaction occurred (no CO_2 was trapped) in the absence of any one of these.

Electrochemistry. Preparative electrolyses were conducted with a Princeton Applied Research Model 173 potentiostat equipped with an Electrosynthesis Model 640 digital coulometer using a single compartment electrochemical cell with a Pt foil working anode and a Pt grid cathode. The solution (prepared with 9.9 mmol of *trans*-1,2-cyclohexanedicarboxylic acid and 0.7 mmol of triethylamine in 40 mL of methanol) was cooled in an ice bath, magnetically stirred, and bubbled with nitrogen during electrolysis. The electrolysis was carried out until 300 C had passed (equivalent to 30% monodecarboxylation). The product mixture was analyzed by GC (HP 5890A) and GC/MS (Finnigan 4023), revealing no monoacid formation or dimerization product.

***trans*-4-Phenylcyclohexanecarboxylic acid (6)** was synthesized by using the method of Johnson and Offenhauer.[36] ^1H NMR (300 MHz, $CDCl_3$): δ 1.57 (m, 4 H), 2.01 (d, J = 13.3 Hz, 2 H), 2.17 (d, J = 13.6 Hz, 2 H), 2.42 (tt, J = 11.8 and 3.5 Hz, 1 H), 2.54 (tt, J = 11.7 and 3.2 Hz, 1 H), 7.26 (m, 5 H). ^{13}C NMR ($CDCl_3$): 29.11, 33.15, 42.76, 43.51, 126.12, 126.71, 128.39, 146.7, 182.24 ppm. MS: m/z 204 (65, M^+), 186 (19), 158 (77), 132 (21), 117 (100), 104 (51), 91 (74), 77 (19). MP: 203-205 °C (lit.[35] mp 203-204 °C).

Mass spectral data of **3-phenylcyclohexanecarboxylic acids 5** were consistent with that of an authentic sample prepared by the method of Rustamov et al.[37]

3-Phenylcyclohexanone (8) was prepared by using a modification of a procedure by House et al.[38] To 5.76 g of CuI (Alfa) was added 30 mL of phenyllithium (2.0 M solution in cyclohexane-ether, Aldrich). The reaction mixture was cooled in an ice bath. A solution of 3.02 g of 2-cyclohexen-1-one (Aldrich) in 50 mL of freshly distilled diethyl ether was added through a dropping funnel so that the temperature never exceeded 10 °C. The mixture was stirred for 15 min after the addition was complete. The reaction mixture was quenched with a solution of saturated aqueous NH_4Cl and ammonia (pH = 8) and air was bubbled through the mixture (to oxidize the insoluble Cu(I) to soluble $Cu(II)NH_3$). The organic layer was combined with the ether extracts of the aqueous layer and was washed with saturated NH_4Cl. The organic layer was dried, concentrated, and distilled at reduced pressure, yielding 0.75 g (13.7%) of 3-phenylcyclohexanone. MS: m/z 174 (100, M^+), 131 (75), 117 (89), 104 (56), 77 (13).

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Stereoselective Nucleophilic Additions to the Carbon-Nitrogen Double Bond. 3. Chiral Acyliminium Ions

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(*S*)-(-)-α-Phenethylamine (**3**), (*S*)-(-)-1-(2-chlorophenyl)ethylamine (**4**), (*S*)-(-)-1-(2,6-dichlorophenyl)ethylamine (**5**), and (*S*)-(-)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine (**6**) have been incorporated into acyliminium ions of structural type **1** and **2**. Five-membered ring acyliminium ion **1d** and six-membered ring acyliminium ion **2c** react with allyltrimethylsilane very stereoselectively. The configurations of the product allyl lactams were determined by chemical correlation with (*S*)-(+)-2-pyrrolidinone-5-acetic acid (**17**) and (*S*)-(+)-2-piperidinone-6-acetic acid (**18**). A transition-state model consistent with molecular orbital theory and substrate conformational preferences is proposed to account for the observed reversal of diastereoselection in the series **1a-d** and **2a-c**.

Acyliminium ions have emerged as an important class of electrophiles which participate in carbon-carbon bond forming reactions.[1] The intramolecular capture of cyclic acyliminium ions by π-bond nucleophiles has proven to be

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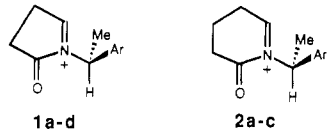
an effective method in the total syntheses of many diverse alkaloids.[2] In contrast, the utilization of *bimolecular* nucleophilic addition reactions to acyliminium ions in alkaloid synthesis has received much less attention.[3] In order to define the stereochemical scope and limitations inherent in such bimolecular addition reactions and to obtain information regarding the transition-state structure of such processes, we have studied and describe herein the allylation reactions of cyclic, chiral acyliminium ions of general structure **1** and **2**.

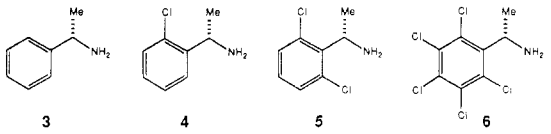


1a-d **2a-c**

a, Ar = phenyl; **b**, Ar = 2-chlorophenyl; **c**, Ar = 2,6-dichlorophenyl; **d**, Ar = 2,3,4,5,6-pentachlorophenyl

At the outset, it was assumed that the degree of stereoselection observed in the nucleophilic addition of allyltrimethylsilane to acyliminium ions **1** and **2** would be governed by steric factors. The single stereogenic center appended to the nitrogen atom of acyliminium ions **1** and **2** creates different steric environments on the two acyliminium ion diastereofaces in the ground state and/or transition state of the nucleophilic addition reaction. It was anticipated that increasing the relative size difference between methyl and aryl groups in acyliminium ions **1** and **2** would selectively increase the steric crowding of one acyliminium ion diastereoface and regularly enhance reaction diastereoselection in the series **1a** → **1d** and **2a** → **2c**.

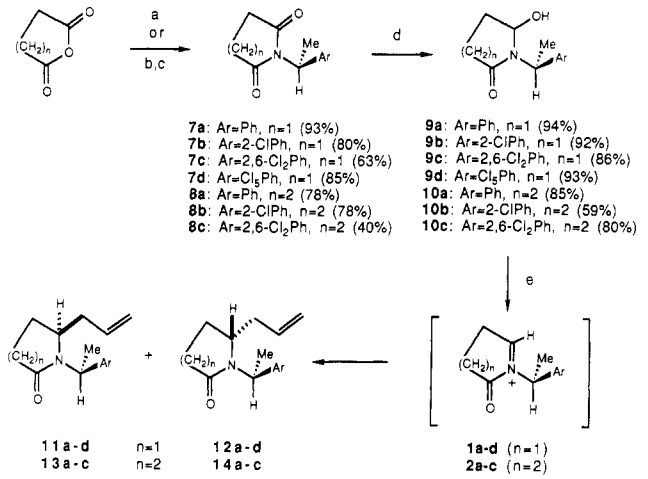
Preparation of Chiral Amines 4–6. (*S*)-(−)-1-(2-Chlorophenyl)ethylamine (**4**) and (*S*)-(−)-1-(2,6-dichlorophenyl)ethylamine (**5**) were prepared from (*S*)-(−)-α-phenethylamine (**3**) as described previously.[4] (*S*)-(−)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine (**6**) was prepared from hexachlorobenzene and resolved. Lithiation[5] of



3 **4** **5** **6**

hexachlorobenzene with *n*-BuLi in THF at −30 °C, followed by addition of *N,N*-dimethylformamide (−78 → −40 °C) afforded pentachlorobenzaldehyde.[6] Reaction of the aldehyde with methyl magnesium bromide at 0 °C produced 1-(2,3,4,5,6-pentachlorophenyl)ethanol[7] in an overall

Scheme I[a]



7a: Ar=Ph, n=1 (93%)
7b: Ar=2-ClPh, n=1 (80%)
7c: Ar=2,6-Cl_2Ph, n=1 (63%)
7d: Ar=Cl_5Ph, n=1 (85%)
8a: Ar=Ph, n=2 (78%)
8b: Ar=2-ClPh, n=2 (78%)
8c: Ar=2,6-Cl_2Ph, n=2 (40%)

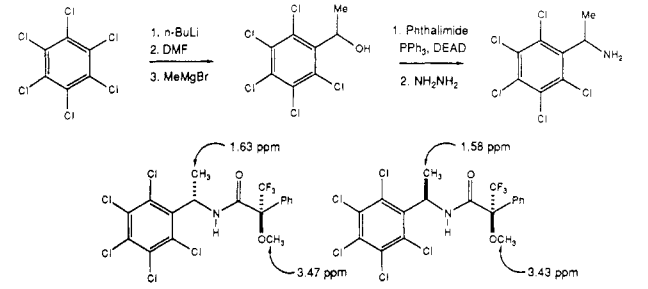
9a: Ar=Ph, n=1 (94%)
9b: Ar=2-ClPh, n=1 (92%)
9c: Ar=2,6-Cl_2Ph, n=1 (86%)
9d: Ar=Cl_5Ph, n=1 (93%)
10a: Ar=Ph, n=2 (85%)
10b: Ar=2-ClPh, n=2 (59%)
10c: Ar=2,6-Cl_2Ph, n=2 (80%)

11a-d n=1 **12a-d**
13a-c n=2 **14a-c**

1a-d (n=1)
2a-c (n=2)

[a] Reagents: (a) (*S*)-(−)-α-phenethylamine (**3**), 180 °C, neat, 2 h; (b) (*S*)-(−)-α-phenethylamine (**3**), (*S*)-(−)-1-(2-chlorophenyl)ethylamine (**4**), (*S*)-(−)-1-(2,6-dichlorophenyl)ethylamine (**5**), or (*S*)-(−)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine (**6**), benzene or neat, 25 °C or 80 °C; (c) 1,1′-carbonyldiimidazole, THF–*n*-Bu_2O, 90 °C, 120 °C, or 135 °C; (d) $LiEt_3BH$, THF, −78 °C; (e) $SnCl_4$, CH_2Cl_2, −22 °C, allyltrimethylsilane.

yield of 55%. Mitsunobu reaction[8] of the carbinol with PPh_3–DEAD–phthalimide (91%) followed by hydrazinolysis[9] (98%) afforded 1-(2,3,4,5,6-pentachlorophenyl)-ethylamine. The amine was then converted to its mandelate salt with (*R*)-(−)-mandelic acid. Three recrystallizations from ethyl acetate–methanol followed by liberation of the free base with 1 N NaOH afforded (*S*)-(−)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine (**6**) of 98% ee. The enantiomeric excess and configuration of the chiral amine were determined by conversion of **6** to the corresponding amide with (*R*)-(+)-MPTA chloride.[10] Comparison of the ^1H NMR spectrum of the amide derived from (*S*)-**6** with that of the amide derived from (*R*)-(+)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine revealed the following chemical shifts. These relative shift patterns are consistent with the configurations assigned to these structures.[10]



Preparation and Allylation of Chiral Acyliminium Ions 1a–d and 2a–c. Direct thermal condensation of succinic or glutaric anhydride with (*S*)-(−)-α-phenethylamine (Scheme I) produced imides **7a**[11] and **8a**[12] in very high yield. The efficiency of the direct thermal conden-

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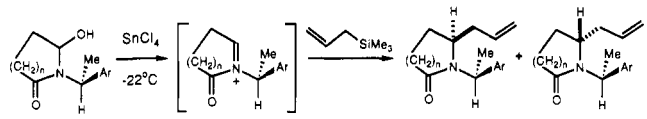
Table I

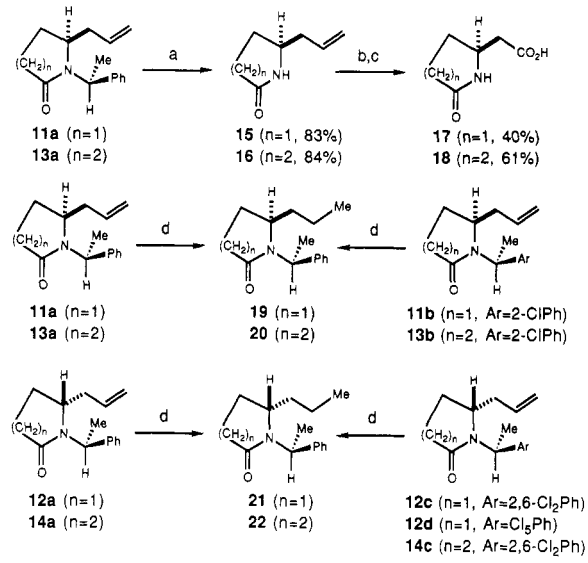


n	Ar	yield,[a] %	ratio[b]
1	Ph (**1a**)	90	82 (**11a**):18 (**2a**)
	2-ClPh (**1b**)	90	71 (**11b**):29 (**12b**)
	2,6-Cl_2Ph (**1c**)	91	9 (**11c**):91 (**12c**)
	Cl_5Ph (**1d**)	91	3 (**11d**):97 (**12d**)
2	Ph (**2a**)	92	83 (**13a**):17 (**14a**)
	2-ClPh (**2b**)	84	67 (**13b**):33 (**14b**)
	2,6-Cl_2Ph (**2c**)	88	2 (**13c**):98 (**14c**)

[a] Combined yield of both diastereomers after purification by flash chromatography. [b] Determined by capillary GC analysis (DB-5, 30 m) and/or HPLC (ISCO 5 μm silica, 254 nm).

sation decreased dramatically upon progressive substitution of the aromatic ring of α-phenethylamine with chlorine atoms. The decrease in condensation efficiency was most likely due to increased steric hindrance and perhaps decreased nitrogen nucleophilicity in the series **3** → **4** → **5** → **6**. In the case of amine **6**, the combined inductive electron withdrawal of five chlorine atoms should reduce the nucleophilicity of the amine nitrogen substantially. Nevertheless, a two-step coupling procedure afforded imides **7b–d** and **8b,c** in adequate to excellent yields. Succinic or glutaric anhydride were reacted with (*S*)-(−)-1-(2-chlorophenyl)ethylamine (**4**), (*S*)-(−)-1-(2,6-dichlorophenyl)ethylamine (**5**), or (*S*)-(−)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine (**6**) to afford intermediate acid amides which were cyclized by heating in the presence of 1,1′-carbonyldiimidazole.[13] It is notable that imide **7d**, derived from the most hindered amine employed, was formed in an overall yield of 85%. Consistent with literature precedent,[14] we observed lower yields in the formation of the six-membered ring imides **8a–c**. The imides were very efficiently reduced to the corresponding hydroxy lactams with lithium triethylborohydride[15] at −78 °C. In most cases, these hydride reductions were highly stereoselective reactions. Reduction of **7a** produced the corresponding hydroxy lactams in a 95:5 ratio, reduction of **7b** afforded hydroxy lactams **9b** in a ratio of 67:33, while reduction of **7c** and **7d** produced a single hydroxy lactam diastereomer. Similar results were obtained in the six-membered ring series. The hydroxy lactams were then reacted with stannic chloride and allyltrimethylsilane[16] in anhydrous dichloromethane at −22 °C. Of several Lewis acids screened ($SnCl_4$, $TiCl_4$, BF_3·Et_2O, Bu_2BOTf, Sn(OTf)$_2$), stannic chloride afforded the optimum balance between reaction stereoselection, rate, and product yield. Under these conditions, the intermediate acyliminium ions **1a–d** and **2a–c** were allylated in high yield (84–92%). The stereoselectivity of these allylation reactions is presented in Table I. The parent acyliminium ions **1a** and **2a** displayed moderate stereoselectivity (~4:1) in the allylation reaction. Interestingly, the diastereoselection decreased

Scheme II[a]



[a] Reagents: (a) excess Na, NH_3, −33 °C, 10 min, then NH_4Cl; (b) O_3, MeOH, −78 °C, 10 min; (c) MeOH, 30% H_2O_2, NaOH; (d) 10% Pd/C, MeOH, HCO_2NH_4.

for acyliminium ions **1b** and **2b**, and the sense of stereoselection reversed for acyliminium ions **1c**, **2c**, and **1d** derived from (*S*)-(−)-1-(2,6-dichlorophenyl)ethylamine or (*S*)-(−)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine.

Determination of Configuration of the Allyl Lactams. The absolute stereostructures of allylation products **11a–d** through **14a–c** were assigned unambiguously by correlation (Scheme II). Diastereomerically pure samples of allyl lactam isomers **11a–d**–**14a–c** were obtained by preparative HPLC on a Dynamax 8 μm silica column, using ethyl acetate–hexane solvent mixtures or by recrystallization. Allyl lactams **11a** and **13a** were reduced[17] with excess sodium in liquid ammonia to lactams **15** (83%) and **16** (84%). These lactams were then ozonized in methanol at −78 °C and oxidized[18] with basic hydrogen peroxide to (*S*)-(+)-2-pyrrolidinone-5-acetic acid[19] (**17**, 40%, $[\alpha]_D$ +20.3° (*c* 0.8, EtOH)) and (*S*)-(+)-2-piperidinone-6-acetic acid[12] (**18**, 61%, $[\alpha]_D$ +17.8° (*c* 1.0, EtOH)).

Allyl lactams **11a** and **13a** were reduced in the presence of 10% palladium on carbon under transfer hydrogenation conditions[20] to propyl lactams **19** (88%) and **20** (78%). Under the same conditions, hydrogenation and concurrent hydrogenolysis of **11b** and **13b**, the major diastereoisomers obtained by allylation of acyliminium ions **1b** and **2b**, occurred producing propyl lactams **19** (85%) and **20** (83%). Diastereomerically homogeneous allyl lactams **12a** and **14a** were similarly reduced[20] to propyl lactams **21** (87%) and **22** (89%). The major allyl lactam diastereoisomers **12c**, **12d**, and **14c** obtained from allylation of chiral acyliminium ions **1c**, **1d**, and **2c** afforded propyl lactams **21** and **22** upon hydrogenation–hydrogenolysis.[20] In further control experiments, the minor isomers **12b**, **14b**, and **11c** were converted stereospecifically to the expected propyl lactams (**21**, **22**, and **19**, respectively) upon hydrogenolysis–hydrogenation. This set of experiments rigorously proved the relative and absolute stereostructures of allylation

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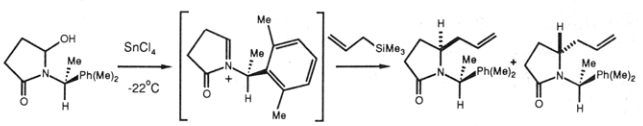
products **11a–d**, **12a–d**, **13a–c**, and **14a–c**.

Discussion

The allylation reactions reported in Table I represent examples of 1,3-asymmetric induction. Interpretation of the stereoselection data in Table I involves determining those acyliminium ion conformers which participate in the allylation reaction, the extent to which they participate, and the diastereofacial preference of each "reactive conformation". Acyliminium ions **1a–d** and **2a–c** possess a carbon–nitrogen double bond embedded in a rather rigid five- or six-membered ring. Two conformational degrees of freedom accessible to these structures are (1) rotation about the C–N single bond linking the nitrogen atom to the stereogenic center, and (2) rotation about the C–C bond linking the (chloro)aromatic moiety to the stereogenic center. The phenyl-substituted acyliminium ions **1a** and **2a** show a modest preference for *re* face nucleophilic attack. Interestingly, when the phenyl group in acyliminium ions **1** and **2** is replaced with the 2-chlorophenyl group the reaction diastereoselection decreases, and the sense of diastereoselection reverses for Ar = 2,6-dichlorophenyl and 2,3,4,5,6-pentachlorophenyl. In quantitative terms, the change in $\Delta\Delta G^{\ddagger}$ observed in the allylation of **1a** (82:18 product ratio) to **1d** (3:97 product ratio) is 2.4 kcal/mol. The progressive reversal in π facial attack experienced by the acyliminium ions **1a** → **1b** → **1c** → **1d** can, in principle, be due to steric and/or electronic factors. At present, it appears that the major factor responsible for the reversal of diastereoselection observed in these reactions is electronic in nature. Support for this hypothesis is provided by the nonselective allylation reaction[21] of acyliminium ion **23** in which the aromatic ring of the chiral directing group is substituted at the 2- and 6-positions with methyl groups. If the stereoselectivity of the allylation reaction were being dictated strictly by group size differences[22] of aryl and methyl moieties in **1a–d**, **2a–c**, and **23**, one would anticipate a stereoselection of allylation of **23** similar to that of **1c**. This is not observed.



23 1:1 ratio

We presume that the allylation reactions reported in Table I are proceeding via discrete acyliminium ion intermediates. We also presume that Curtin–Hammett kinetics[23] are operative in this reaction system. That is, the energy barrier of interconversion of the "reactive conformations" participating in the allylation reaction is lower than the free energy of activation for the reaction.

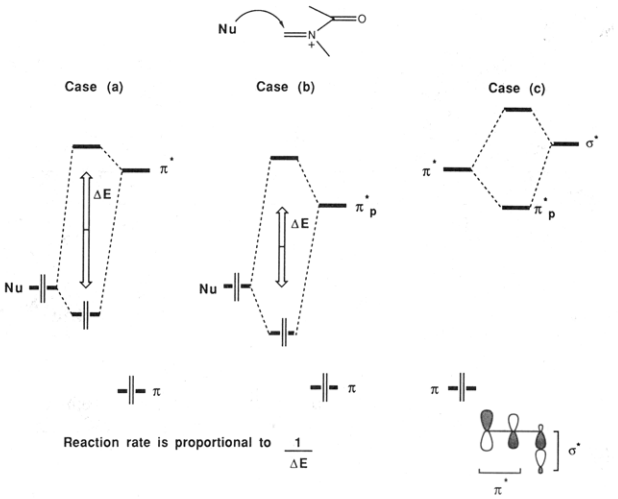


Figure 1.

By analogy to nucleophilic addition reactions to carbonyl compounds,[24] one can invoke an electronic effect of an allylic stereogenic center on an addition reaction to a trigonal carbon atom by consideration of the overlap of a properly aligned orbital with the π system undergoing attack (Figure 1). Frontier molecular orbital theory states[25] that one term contributing to the transition-state stabilization associated with the encounter of two reacting species is inversely proportional to the energy difference between the closest energy pair of interacting frontier orbitals. For the allylation reactions of Table I, the important frontier orbitals are the HOMO of the allylsilane and the LUMO of the acyliminium ion (represented simply as π^* in case a of Figure 1). If orbital overlap between a properly aligned, allylic σ^* orbital and the π^* orbital occurs, two new "perturbed" molecular orbitals are obtained. Such orbital mixing results in a lowering of the energy of the LUMO, illustrated as case c, Figure 1. Hence, a conformation with such an orbital overlap possesses a smaller frontier orbital energy gap in its reaction with a given nucleophile (case b, Figure 1). The smaller frontier orbital energy gap produces greater transition-state stabilization and implies a smaller free energy of activation for reaction of that conformer relative to others, hence it should react faster. Therefore, certain conformations can contribute to the observed ratio of product diastereomers to a greater extent than other less reactive conformations. Thus, in systems capable of free rotation such as **1** and **2**, frontier molecular orbital theory provides an electronic mechanism for establishing a transition state "conformational bias" on the otherwise freely rotating phenethyl moiety by σ^*–π^* overlap. In this regard, it is important to point out that maximum perturbation (energy lowering) of π^* will occur by interaction of π^* with that allylic σ^* closest in energy to π^*.

Given this aza analogue of the Anh hypothesis,[24a] it is instructive to consider several situations possible in a chemical reaction. In one limit, the π^* orbital energy is widely separated from the energies of all three π^* orbitals emanating from the stereogenic center. In this instance, the electronic nature of the groups attached to the stereogenic center has little influence, and reaction stereoselection is dominated by transition-state steric effects. These transition-state steric effects represent a sum of

(21) Polniaszek, R. P.; Belmont, S. E., unpublished results.

(22) The (aryl)–Cl and (aryl)–CH_3 bond lengths are 1.70 and 1.51 Å, respectively. The van der Waals radii of Cl and CH_3 are 1.80 and 2.0 Å, respectively: Gordon, A. J.; Ford, R. A. *The Chemists Companion*; Wiley: New York, 1972. Consequently, the aryl groups in acyliminium ions **7c** and **23** should possess approximately the same effective size. In fact, measurement of the relative effective size of methyl and chlorine substituents as structural elements of molecules enabling a direct comparison of aryl–CH_3 and aryl–Cl bonds indicate that in these systems, a methyl group behaves chemically as if it is slightly larger than a chlorine group: Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5299. Stoughton, R. W.; Adams, R. *J. Am. Chem. Soc.* **1932**, *54*, 4426. Yuan, H. C.; Adams, R. *J. Am. Chem. Soc.* **1932**, *54*, 4434. On this basis, one would predict that acyliminium ion **23** should possess a larger aryl moiety than acyliminium ion **7c**.

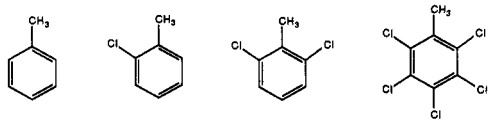
(23) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; American Chemical Society: Washington, DC, 1981; pg 28.

(24) (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1987**, *109*, 908.

(25) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976; pp 27–32.

intramolecular effects (conformational energy) and intermolecular steric effects. At the other limit, the π^* orbital is very close in energy to one of the σ^* orbitals emanating from the stereogenic center, and this substituent is effective at establishing a preferred transition-state conformation. In between these two extremes is a situation wherein transition-state steric effects will compete with or enforce the stereoelectronic transition-state conformational bias promoted by σ^*–π^* overlap.

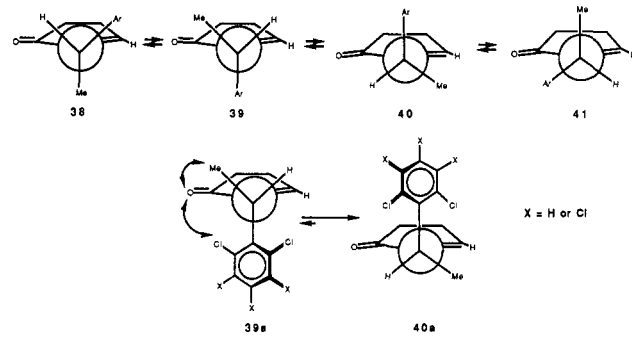
In the frontier molecular orbital analysis, the key to understanding the stereoselection data in Table I is determining that σ^* orbital emanating from the stereogenic center in **1a–d** and **2a–c**, which is closest in energy to π^* and hence will produce maximum transition-state stabilization. In order to gain insight into the effect of chlorine substitution on this crucial σ^* orbital energy, we carried out MNDO calculations[26] on toluenes **24–27**. Using the SYBYL computer program,[27] the geometries of structures **24–27** were optimized with the MAXIMIN molecular mechanics package. Using these optimized geometries, we carried out single point MNDO energy calculations, which generated the molecular orbitals and associated eigenvalues.



24 **25** **26** **27**

It must be remembered that molecules are best described by molecular orbitals, and the simplistic assumption of a localized bond description of a σ^* orbital may not be rigorously correct. Rather, the total antibonding character between two atomic centers may contain contributions from more than one molecular orbital. Listed in Table II are the coefficients and energies of the most significant contributors to what can be considered the (aryl)–CH_3 σ^* orbital in **24–27**. We presume the largest contribution to this σ^* orbital will arise from that MO which possesses the largest magnitude of antibonding character between C_1 and C_2 as measured by the product of p_x atomic orbital coefficients in the relevant molecular orbitals. The greater the magnitude of this product, the greater the antibonding character between C_1 and C_2. Employing this reasoning, σ^* decreases regularly (4.78 → 4.27 → 4.04 → 3.04 eV) in the series **24** → **27**.

The picture which emerges from these calculations is that acyliminium ion **1a** is presumably reacting via several independent conformations, of which four, **38–41**, are shown below. Presumably these conformers are not equally populated, and each conformer is associated with its own distinct diastereofacial preference toward nucleophilic attack. The observed ratio of allyl lactams **11a:12a** listed in Table I is the sum of contributions to the overall reaction from (at least) conformers **38–41** (Ar = Ph). Upon chlorination of the aryl moiety in acyliminium ion **1a**, reaction via conformers such as **39** and **40** becomes increasingly favored electronically. The σ^* (aryl–C) orbital energy is decreasing regularly in the series **1a–d**, leading to a regularly decreasing π_p^* orbital energy (Figure 1) in conformers such as **39** and **40**. This produces an increased percentage of reaction arising via kinetically preferred nucleophilic addition to conformers **39** and/or **40**. In addition to the electronic component of transition-state



38 **39** **40** **41**

39a **40a**

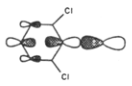
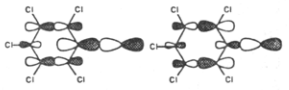
stabilization, it is also necessary to consider more subtle steric interactions present within these conformers. Thus, conformer **39** suffers a gauche (carbonyl) oxygen ↔ methyl interaction, and other factors being equal, should be disfavored energetically relative to conformer **40**. A wide body of data suggests[28] that 2,6-ortho-disubstituted aromatic rings which possess a $CH(R_1)(R_2)$ substituent at the one position strongly favor conformations in which the hydrogen attached to the benzylic center eclipses one of the two ortho substituents. Thus, for acyliminium ions **1c** and **1d**, if such a conformational preference manifests itself in **39** and **40** the result is conformers **39a** and **40a**, in which the aryl moiety is now twisted. Conformer **39a** is further disfavored energetically relative to **40a**, in that **39a** experiences a nonbonded steric interaction between the carbonyl oxygen of the acyliminium ion and an ortho chlorine substituent of the aromatic ring.

Given that conformer **40a** possesses fewer steric interactions than conformer **39a**, we predict that this is the predominant reactive conformation of acyliminium ions **1c** and **1d**. Nucleophilic attack occurs anti to the aryl moiety in this conformer, giving rise to allyl lactams **12c** and **12d** as major products. Similar arguments can explain the trend in stereoselection observed with six-membered ring acyliminium ions **2a–c**.

The frontier molecular orbital analysis presented in Figure 1 in tandem with the MNDO calculations cited in Table II provide a working model for understanding the *trend* in stereoselection observed in the series **1a–d**. The selective *re* diastereofacial attack experienced by **1a** and **1b** appears at first sight inconsistent with this analysis. However, the magnitude of transition-state stabilization afforded by σ^*–π^* overlap is critically dependent upon the energy difference between the interacting molecular orbitals. The observed diastereofacial selectivity in the reaction of **1a** suggests that the energy gap between π^* and any of the three σ^* orbitals emanating from the stereogenic center is too large to provide enough transition state stabilization to overcome the (steric effect dominated) transition-state topological preference of the **1a**–allyltrimethylsilane reactant pair. However, upon perchlorination of the aromatic ring, the energy of one σ^* orbital is selectively decreased. Upon introduction of one chlorine atom to the aromatic ring, the *re* face diastereofacial selection of **1b** begins to decrease, and introduction of two chlorine atoms lowers the σ^* energy further, resulting in a greater percentage of reaction occurring via conformer **40a**, and net reversal of stereoselection. If this analysis is correct, then acyliminium ions **1a–d** represent a fascinating system in that the electronics of the system have been manipulated in such a way as to proceed from a situation wherein the σ^*–π^* stereoelectronic control ele-

(26) Dewar, M. J. S.; Theil, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. Dewar, M. J. S.; Rzepa, H. S. *J. Comp. Chem.* **1983**, *4*, 158.
(27) Distributed by Tripos Associates, St. Louis, MO.
(28) Berg, U.; Liljefors, T.; Roussel, C.; Sandstrom, J. *Acc. Chem. Res.* **1985**, *18*, 80. Price, R.; Schilling, G.; Ernst, L.; Mannschreck, A. *Tetrahedron Lett.* **1972**, 1689.

Table II

	Toluene[a]		2-Chlorotoluene[a]	
				
$(C_1)(C_2)$[b]	0.08	0.12	0.19	0.05
Energy (eV)	4.40	4.78	4.27	4.58
	Orbital Coefficients[c]		Orbital Coefficients[c]	
C_1	-0.36	-0.41	-0.52	0.21
C_2	-0.23	-0.30	-0.36	0.23
C_3	-0.04	0.17	0.08	0.07
C_4	0.14	0.01	0.14	0.17
C_5	0.28	0.22	0.23	-0.29
C_6	0.14	0.01	0.01	-0.11
C_7	-0.04	0.17	-0.04	-0.25
	2,6-Dichlorotoluene[a]		Pentachlorotoluene[a]	
				
$(C_1)(C_2)$[b]	0.26		0.28	0.07
Energy (eV)	4.04		3.04	4.13
	Orbital Coefficients[c]		Orbital Coefficients[c]	
C_1	-0.60		0.57	0.47
C_2	-0.44		0.49	0.15
C_3	0.01		0.23	-0.36
C_4	0.06		0.26	-0.21
C_5	0.27		-0.10	0.11
C_6	0.08		0.26	-0.20
C_7	0.02		0.24	-0.37

[a] The qualitative diagrams of the relevant molecular orbitals contain only those p_x orbitals with coefficient magnitudes ≥0.1. [b] The product of coefficients of p_x atomic orbitals between centers C1 and C2. [c] For p_x orbitals. The geometry of the molecules is defined with carbon 1 at the origin, carbon 2 lying along the x axis, and the p_z orbitals which comprise the π system lying along the z axis.

ment plays either a small role (**1a,b**) in diastereofacial selection to one in which it plays a dominant role (**1d**) in stereoselection.

Conclusions

In summary, we have studied the reactions of five- and six-membered ring acyliminium ions with allyltrimethylsilane. We observed an interesting reversal of diastereoselection in the series **1a–d** and **2a–c**. Our results can be rationalized by application of molecular orbital theory and selection of locally preferred substrate conformational preferences. The apparent effect of perchlorination of the aromatic ring in acyliminium ions **1** is to selectively stabilize nucleophilic addition transition states which possess a substrate geometry similar to **40a**. The regular trend in stereoselectivity in the series **1a–d** is reflected in the trend of σ^* orbital energies in the series **24** → **27**.

The high precision associated with nucleophilic addition to acyliminium ions **1d** and **2c** represents a synthetically useful level of stereoselection. Consequently, we are pursuing more direct routes to amine **6** and will apply these and related reactions in enantioselective total syntheses of alkaloids.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^1H NMR spectra were recorded on a Varian XL-300 (300 MHz) spectrometer. Data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the delta scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublet of doublets, td = triplet of doublets), integration, coupling (in hertz), and interpretation. ^{13}C NMR spectra were recorded on a Varian XL-300 (75 MHz) spectrometer. Mass spectra were determined on a HP-5988A mass spectrometer operating at 70 eV. Combustion analyses were performed by Spang Microanalytical Laboratory (Eagle Harbor, MI). Analytical gas–liquid chromatography (GC) was carried out on a Hewlett-Packard 5890A chromatograph, using a 30 m × 0.32 mm fused silica capillary column wall coated with DB-5. Dichloromethane was distilled from calcium hydride prior to use. Tetrahydrofuran and di-*n*-butyl ether were distilled from sodium benzophenone prior to use. Liquid ammonia was distilled from sodium prior to use. Flash chromatography was carried out with Kieselgel 60 (230–400 mesh) silica gel. All reactions were run under a nitrogen atmosphere. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at a temperature of 22 °C and a wavelength of 589 nm.

1-(2,3,4,5,6-Pentachlorophenyl)ethanol.[7] A solution of *n*-BuLi (4.6 mL, 10.1 mmol, 2.2 M in hexane) was added dropwise to a precooled (−30 °C) suspension of hexachlorobenzene (2.85 g, 10.0 mmol) in THF (100 mL) with stirring. The resulting brown mixture was stirred at −30 °C for 10 min and cooled to −78 °C, and neat DMF (1.5 mL, 1.9 equiv) was added. After 5 min, the solution was gradually warmed to −40 °C and, after 15 min at this temperature, was quenched with 1 N HCl (50 mL) and warmed to room temperature. The mixture was extracted with EtOAc and then CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford a yellow solid. The solid was triturated with hot hexane and filtered through a short plug of glass wool, and the filtrate was concentrated to afford a yellow solid, 2.38 g. This solid, which contained pentachlorobenzaldehyde[6] and hexachlorobenzene, could be purified with difficulty by silica gel chromatography. In practice, it proved much easier to sublime the mixture, carrry out the next step, and purify the 1-(2,3,4,5,6-pentachlorophenyl)ethanol.

The mixture was sublimed (120–130 °C, 0.01 mmHg) to afford a nearly colorless solid. The solid was dissolved in THF (40 mL) and cooled to 0 °C. A solution of methylmagnesium bromide (2.95 mL, 1 equiv, 2.9 M in THF) was added dropwise. After 1 h at 0 °C, the reaction was quenched by addition of 1 N HCl and then water. Enough EtOAc was added to dissolve the precipitated organic material, and the aqueous and organic layers were separated. The aqueous layer was extracted two more times (CH_2Cl_2), and the combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was flash chromatographed on silica gel with a gradient of 5:95 → 10:90 → 20:80 EtOAc–Hex, affording 1-(2,3,4,5,6-pentachlorophenyl)ethanol as a white solid: 1.64 g, 55.7%; mp 123–124 °C (lit.[7] mp 126 °C); IR (CH_2Cl_2) 1700 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (dq, 1 H, J = 10, 7, CH), 2.85 (d, 1 H, J = 10, OH), 1.63 (d, 3 H, J = 7, CH_3); ^{13}C NMR (75 MHz, acetone-d_6) δ 142.6, 132.9, 132.7, 132.5, 69.1, 20.2; mass spectrum (trimethylsilyl ether derivative, Cl, NH_3), m/e 364 (M^+, ^{35}Cl).

***N*-(1-(2,3,4,5,6-Pentachlorophenyl)ethyl)phthalimide.** A solution of diethyl azodicarboxylate (1.17 g, 1.2 equiv) in THF (15 mL) was added dropwise to a cold (5 °C) solution of 1-(2,3,4,5,6-pentachlorophenyl)ethanol (1.64 g, 5.6 mmol), triphenylphosphine (1.76 g, 1.2 equiv), and phthalimide (0.99 g, 1.2 equiv) in THF (30 mL) with stirring over 20 min. The solution was warmed to room temperature and stirred overnight. After 18 h, the solvent was removed on a rotary evaporator. The residue was flash chromatographed on silica gel with the gradient 10:90 → 15:85 → 20:80 EtOAc–Hex. The imide was obtained as a white solid: 2.22 g, 91%; mp 193–195 °C; IR (CH_2Cl_2) 1780 (m), 1740 (m), 1715 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81–7.65 (m, 4 H, ArH_4), 6.05 (q, 1 H, J = 7.5, ArCH), 2.06 (d, 3 H, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 137.4, 134.2, 133.1, 132.7, 131.9, 131.4, 123.2, 52.9, 15.3; mass spectrum (Cl, CH_4), m/e 422 (MH^+, ^{35}Cl). Anal. Calcd for $C_{16}H_8Cl_5NO_2$: C, 45.38; H, 1.90. Found: C, 45.59; H, 1.84.

1-(2,3,4,5,6-Pentachlorophenyl)ethylamine. Hydrazine hydrate (1.2 mL, 7.5 equiv) was added to a solution of 1-(2,3,4,5,6-pentachlorophenyl)ethylphthalimide (2.15 g, 5.0 mmol) in THF (75 mL) and EtOH (12 mL) with stirring. After 18 h, the suspension was heated to 70 °C. After 11 h, the mixture was filtered, the solid was thoroughly washed with THF, and the

solvent was removed from the filtrate on a rotary evaporator. The solid residue was dissolved in $CHCl_3$; the solution placed atop 1.5 in. × 9 in. of silica gel and eluted with the gradient EtOAc → 2:98 → 5:95 MeOH–EtOAc. The amine was obtained as a white solid: 1.44 g, 98%; mp 87–88 °C; IR (CH_2Cl_2) 3400 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.99 (q, 1 H, J = 7, NC*H*CH_3Ar) 2.0 (br s, 2 H, NH_2), 1.54 (d, 3 H, J = 7, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 132.1, 131.7, 51.2, 20.7; mass spectrum (Cl, NH_3), m/e 292 (MH^+, ^{35}Cl). Anal. Calcd for $C_8H_6Cl_5N$: C, 32.75; H, 2.06. Found: C, 32.78; H, 1.95.

(*S*)-(−)-1-(2,3,4,5,6-Pentachlorophenyl)ethylamine (6). The amine (1.44 g) and (*R*)-(−)-mandelic acid (0.75 g, $[\alpha]_D$ −153° [*c* 2.5, H_2O]) were dissolved in a hot mixture of EtOAc (100 mL) and MeOH (2 mL). The solution was stored in a freezer at −15 °C for 4 days. The cold supernatant liquid was cannulated away from the white globular crystals, and the crystals were recrystallized from EtOAc (50 mL) and MeOH (1 mL). After 3 days at −15 °C, the supernatant was cannulated away from the white crystals. The crystals were collected and dried, affording 0.86 g of the amine–mandelate salt. This salt was suspended in CH_2Cl_2 (20 mL) and 1 N NaOH (20 mL), and the mixture was stirred for 35 min. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated, affording a clear oil which gradually solidified: 531.7 mg, 78% of (*S*)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine (**6**). This material displayed the same analytical data as racemic material, except mp 59–60 °C. The α-methoxy-α-phenyl-α-(trifluoromethyl)acetamide of this material prepared from (*R*)-(+)-MPTA chloride[10] was analyzed by HPLC (5 μm silica, 5:95 EtOAc–Hex, 2 mL/min) to reveal a diastereomeric ratio of 97.5:2.5. The major isomer (derived from (*S*)-**6**) displayed the ^1H NMR spectrum (300 MHz, $CDCl_3$) δ 7.67 (d, 1 H, J = 7.5, NH), 7.40–7.22 (m, 5 H, ArH_5), 6.02 (qn, 1 H, J = 7.5, CH), 3.47 (s, 3 H, OCH_3), 1.63 (d, 3 H, J = 7.5, CHC*H*$_3$). (A third recrystallization of the amine mandelate salt afforded the salt $[\alpha]_D$ −42.1° (*c* 1.3, MeOH), which upon basification provided (*S*)-**6**: $[\alpha]_D$ −3.4° (*c* 1, CH_2Cl_2), 98% ee.)

The solvent from the mother liquor from the first recrystallization was removed on a rotary evaporator. The residue was dissolved in a large volume of ether and extracted three times with 1 N HCl. The amine hydrochloride salt was insoluble in water. Thus, a suspension of the hydrochloride in 1 N HCl was formed. The suspension was separated from the ethereal layer with each extraction. The combined aqueous extracts were cooled to 0 °C and basified to pH 13 with solid KOH, and extracted (3×, CH_2Cl_2). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated, affording (*R*)-**6** as a waxy oil: 530.9 mg, 74%. The α-methoxy-α-phenyl-α-(trifluoromethyl)acetamide of this material prepared from (*R*)-(+)-MPTA chloride[10] was analyzed by HPLC (5 μm silica, 5:95 EtOAc–Hex, 2 mL/min) to reveal a diastereomeric ratio of 92:8. The major isomer (derived from (*R*)-**6**) displayed the ^1H NMR spectrum (300 MHz, $CDCl_3$) δ 7.75 (d, 1 H, J = 7.5, NH), 7.60–7.36 (m, 5 H, ArH_5), 6.05 (qn, 1 H, J = 7.5, CH), 3.43 (s, 3 H, OCH_3), 1.58 (d, 3 H, J = 7.5, CHC*H*$_3$); mass spectrum (Cl, NH_3), m/e 508 (MH^+).

The ethereal layer from the 1 N HCl extraction of material derived from the mother liquor of the first recrystallization of the amine–mandelate salt afforded a yellow solid after drying (Na_2SO_4), filtration, and solvent removal. Recrystallization of the solid from EtOAc–Hex afforded ***N*-(1-(2,3,4,5,6-pentachlorophenyl)ethyl)acetamide** as a while solid: 90 mg; mp 213–214 °C; IR (CH_2Cl_2) 3450 (w), 1680 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (d, 1 H, J = 7.5, NH), 5.97 (qn, 1 H, J = 7.5, CH), 1.97 (s, 3 H, $COCH_3$), 1.55 (d, 3 H, CHC*H*$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.7, 140.5, 131.4, 131.0, 48.5, 21.9, 16.4; mass spectrum (Cl, NH_3), m/e 334 (MH^+, ^{35}Cl).

1-((1*S*)-1-(2,3,4,5,6-Pentachlorophenyl)ethyl)succinimide (7d). A mixture of amine **6** (131 mg, 1.03 mmol) and succinic anhydride (446 mg, 10 equiv) were heated at 110 °C for 24 h. Upon cooling, the residue was dissolved in ether and extracted twice with saturated $NaHCO_3$. The combined base extracts were acidified with concentrated HCl and extracted five times with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated, affording the intermediate acid amide as a white solid: 161 mg, 92%; mp 134–135 °C; IR (CH_2Cl_2) 3600–2300 (br), 3450 (w), 1715 (s), 1680 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (br s, 1 H, CO_2H), 6.69 (s, 1 H, J = 7.5, NH), 6.02 (qn, 1 H, J = 7.5, NHC*H*), 2.76–2.42 (m, 4 H, CH_2CH_2), 1.60 (d, 3 H, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 171.0, 138.5, 132.9, 48.4, 30.3, 29.2, 17.6; mass spectrum (Cl, NH_3), m/e 392 (MH^+, ^{35}Cl); $[\alpha]_D$ +18.8° (*c* 0.9, CH_2Cl_2). Anal. Calcd for $C_{12}H_{10}Cl_5NO_3$: C, 36.63; H, 2.56. Found: C, 36.61; H, 2.62. The acid amide (109 mg, 0.28 mmol) was suspended in n-Bu_2O (5 mL), a solution of 1,1′-carbonyldiimidazole (65 mg, 1.5 equiv) in THF (6 mL) was added, and the reaction was heated at 120 °C for 24 h. An additional 1.5 equiv of 1,1′-carbonyldiimidazole in THF (3 mL) was added, and the heating was continued at 120 °C. After 72 h, the solution was cooled to room temperature and directly flash chromatographed on silica with 20:80 EtOAc–Hex, affording **7d** as a white solid: 95.6 mg, 92%; mp 182–183 °C; IR (CH_2Cl_2) 1785 (w), 1715 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (q, 1 H, J = 7.5, ArCH), 2.68 (s, 4 H, CH_2CH_2), 1.92 (d, 3 H, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 137.1, 133.2, 132.9, 131.8, 53.7, 28.2, 15.1; mass spectrum (Cl, NH_3), m/e 374 (MH^+, ^{35}Cl); $[\alpha]_D$ +255.0° (*c* 1.2, CH_2Cl_2). Anal. Calcd for $C_{12}H_8Cl_5NO_2$: C, 38.39; H, 2.15. Found: C, 38.46; H, 2.11.

1-((1*S*)-1-(2,6-Dichlorophenyl)ethyl)glutarimide (8c). A mixture of amine **5** (500 mg, 2.6 mmol) and glutaric anhydride (330 mg, 2.9 mmol) were heated at 100 °C for 36 h. Upon cooling, trituration with benzene afforded the intermediate acid amide as a white solid: 673 mg, 84%; mp 134–136 °C; IR ($CHCl_3$) 3450 (w), 3400–2300 (br), 1715 (s), 1675 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, 2 H, J = 8, ArH_2), 7.10 (t, 1 H, J = 8 Hz, ArH), 6.54 (d, 1 H, J = 7.5, NH), 5.99 (qn, 1 H, J = 7.5, ArCH), 2.40 (t, 2 H, J = 7, CH_2), 2.29 (td, 2 H, J = 7, 3.5, CH_2), 1.95 (qn, 2 H, J = 7, $NCOCH_2CH_2$), 1.54 (d, 3 H, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 171.5, 137.4, 134.4, 129.4, 128.8, 46.3, 35.2, 33.1, 20.5, 18.7; mass spectrum (Cl, NH_3), m/e 304 (MH^+, ^{35}Cl); $[\alpha]_D$ +62.1° (*c* 1.2, EtOH). Anal. Calcd for $C_{13}H_{15}Cl_2NO_3$: C, 51.33; H, 4.97. Found: C, 51.45; H, 4.96. Imide **8c** was prepared from this acid amide according to the procedure for **7d**, affording a white solid: 48%; mp 104–105 °C; IR (CH_2Cl_2) 1735 (m), 1685 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, 2 H, J = 8, ArH_2), 7.08 (t, 1 H, J = 8, ArH), 6.05 (q, 1 H, J = 7.5, ArCH), 2.62 (t, 2 H, J = 6, CH_2), 2.61 (t, 2 H, J = 6, CH_2), 1.90 (qn, 2 H, J = 6, C_4-H_2), 1.88 (d, 3 H, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 136.5, 135.0, 129.7, 128.4, 51.6, 33.7, 19.0, 17.2; mass spectrum (Cl, NH_3), m/e 286 (MH^+, ^{35}Cl); $[\alpha]_D$ −254.5° (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{13}H_{13}Cl_2NO_2$: C, 54.57; H, 4.58. Found: C, 54.57; H, 4.62.

5-Hydroxy-1-((1*S*)-1-(2,3,4,5,6-pentachlorophenyl)-ethyl)-2-pyrrolidinone (9d). A solution of lithium triethylborohydride (0.47 mL, 0.47 mmol, 1.0 M in THF) was added to a solution of imide **7d** (111 mg, 0.30 mmol) in THF (9 mL) with stirring at −78 °C. After 40 min, the mixture was quenched with saturated $NaHCO_3$ (4 mL) and warmed to 0 °C, 30% H_2O_2 (5 drops) was added, and the mixture was stirred at 0 °C. After 20 min, the THF was removed on a rotary evaporator, and the aqueous residue was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated, and the residue was flash chromatographed with EtOAc, affording a white solid (single diastereomer by ^1H NMR; configuration at C_5 not determined): 104 mg, 93%; mp 180–181 °C; IR (CH_2Cl_2) 1705 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (q, 1 H, J = 7.5, ArCH), 5.69 (m, 1 H, C_5-H), 2.62 (m, 1 H), 2.42 (d, 1 H, J = 7.5, OH), 2.45–2.25 (m, 2 H), 2.07 (m, 1 H), 1.75 (d, 3 H, J = 7.5, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 178.1, 141.0, 133.0, 84.1, 53.2, 30.0, 29.4, 14.3; mass spectrum (Cl, NH_3), m/e 376 (MH^+, ^{35}Cl); $[\alpha]_D$ +180.6° (*c* 1.1, CH_2Cl_2). Anal. Calcd for $C_{12}H_{10}Cl_5NO_2$: C, 38.18; H, 2.67. Found: C, 38.23; H, 2.66.

1-((1*S*)-1-(2,6-Dichlorophenyl)ethyl)-6-hydroxy-2-piperidinone (10c). From imide **8c** (34 mg, 0.12 mmol) and $LiEt_3BH$ (0.19 mL, 1.5 equiv) in THF (4 mL) at −78 °C: white solid (single diastereomer by ^1H NMR; configuration at C_6 not determined); 27.3 mg; 80%; mp 155–156 °C; IR (CH_2Cl_2) 1650 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 2 H, J = 8, ArH_2), 7.04 (t, 1 H, J = 8, ArH), 5.84 (q, 1 H, J = 7.5, ArCH), 5.52 (td, 1 H, J = 7, 3.5, C_6-H), 2.45 (m, 1 H, C_3-H_a), 2.29 (m, 1 H, C_3-H_b), 2.24, (d, 1 H, J = 7, OH), 2.18–1.99 (m, 3 H), 1.77 (m, 1 H), 1.69 (d, 3 H, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 138.7, 133.8, 129.2, 127.8, 77.2, 52.5, 32.4, 30.1, 15.1, 14.7; mass spectrum (Cl, NH_3), m/e 288 (MH^+, ^{35}Cl); $[\alpha]_D$ +183.6° (*c* 0.9, CH_2Cl_2).

Anal. Calcd for $C_{13}H_{15}Cl_2NO_2$: C, 54.18; H, 5.25. Found: C, 54.25; H, 5.16.

(5*R*)-(+)-1-((1*S*)-1-(2,3,4,5,6-Pentachlorophenyl)ethyl)-5-(1-prop-2-enyl)-2-pyrrolidinone (12d). Lactam **9d** (65 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (8 mL) and cooled to −78 °C. Allyltrimethylsilane (58 mg, 3 equiv) and tin(IV) chloride (0.26 mL, 1.5 equiv, 1.0 M in CH_2Cl_2) were added sequentially, and the mixture was warmed to −22 °C. After 12 h, the solution was quenched with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel with 50:50 EtOAc–Hex, affording a white solid: 63 mg, 91%. HPLC analysis (ISCO 5 μm silica, 2 mL/min, 50:50 EtOAc–Hex) revealed a 97.2:2.8 ratio of diastereomers. A single recrystallization from hexane afforded pure **12d**: mp 142–143 °C; IR (CH_2Cl_2) 1685 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1 H, C_7-H), 5.65 (q, 1 H, J = 7.5, ArCH), 5.19 (br d, 1 H, J = 17, C=CH*H*, trans), 5.18 (br d, 1 H, J = 10.5, C=C*H*H cis), 4.03 (m, 1 H, C_5-H), 2.51–2.09 (m, 5 H), 1.94 (m, 1 H), 1.64 (d, 3 H, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 139.6, 133.4, 132.3, 118.8, 57.1, 51.9, 39.1, 29.5, 24.1, 14.8; mass spectrum (Cl, NH_3), m/e 400 (MH^+, ^{35}Cl); $[\alpha]_D$ +160.9° (c 1.2, CH_2Cl_2). Anal. Calcd for $C_{15}H_{14}Cl_5NO$: C, 44.87; H, 3.51. Found: C, 45.01; H, 3.41.

(6*R*)-(+)-1-((1*S*)-1-(2,6-Dichlorophenyl)ethyl)-6-(1-prop-2-enyl)-2-piperidinone (14c). From hydroxy lactam **8c** (40 mg, 0.14 mmol), allyltrimethylsilane (48 mg, 3 equiv), and $SnCl_4$ (0.21 mL, 1.5 equiv, 1.0 M in CH_2Cl_2) in CH_2Cl_2 (6 mL): 38 mg, 88%; 98:2 diastereomeric ratio by capillary GC (DB-5, 200 °C, 25 psi). A single recrystallization from hexane afforded diastereomerically pure **14c**: mp 94–95 °C; IR (CH_2Cl_2) 1640 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 2 H, J = 8, ArH_2), 7.03 (t, 1 H, J = 8, ArH), 5.80 (q, 1 H, J = 7.5, ArCH), 5.76 (m, 1 H, C_8-H), 5.20–5.10 (m, 2 H, C=CH_2), 3.86 (m, 1 H, C_6-H), 2.54–2.20 (m, 4 H), 2.00–1.86 (m, 3 H), 1.73 (m, 1 H), 1.62 (d, 3 H, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 139.1, 134.1, 129.1, 127.7, 117.9, 52.6, 38.9, 31.3, 24.2, 15.8, 14.9; mass spectrum (Cl, NH_3), m/e 312 (MH^+, ^{35}Cl); $[\alpha]_D$ +189.7° (c 1.1, CH_2Cl_2). Anal. Calcd for $C_{16}H_{19}Cl_2NO$: C, 61.55; H, 6.13. Found: C, 61.34; H, 6.14.

(5*S*)-(+)-5-(1-Prop-2-enyl)-2-pyrrolidinone (15). A solution of lactam **11a** (55.5 mg, 0.24 mmol) in THF (3 mL) was added to a solution of sodium (17 mg, 0.73 mmol) in anhydrous ammonia (10 mL) at −33 °C. After 10 min, the mixture was quenched by the slow addition of solid NH_4Cl (50 mg, 4 equiv). The ammonia was evaporated, and the residue was dissolved in ether, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed with 5:95 MeOH–EtOAc, affording a clear oil: 25 mg, 83%; IR (NaCl) 3250 (br), 1700 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.94 (s, 1 H, NH), 5.75 (m, 1 H, C_7-H), 5.18–5.10 (m, 2 H, C=CH_2), 3.71 (qn, 1 H, J = 7, C_5-H), 2.38–2.12 (m, 5 H), 1.78 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 133.5, 118.2, 53.8, 40.8, 30.2, 26.4; mass spectrum (Cl, NH_3), m/e 126 (MH^+); $[\alpha]_D$ +4.1° (c 0.65, CH_2Cl_2).

(6*S*)-(−)-6-(1-Prop-2-enyl)-2-piperidinone (16). From lactam **13a** (148 mg, 0.61 mmol), sodium (42 mg, 3 equiv), and ammonia (15 mL): white solid; 71 mg, 84%; mp 82–84 °C; IR (CCl_4) 3200 (br), 1675 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (s, 1 H, NH), 5.71 (dddd, 1 H, J = 16.5, 11, 8.5, 6, C_8-H), 5.16 (br d, 1 H, J = 11, C=C*H*H, cis), 5.15 (br d, 1 H, J = 16.5, C=CH*H*, trans), 3.38 (m, 1 H, C_6-H), 2.44–2.20 (m, 3 H), 2.10 (m, 1 H), 1.90 (m, 2 H), 1.68 (m, 1 H), 1.37 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 133.4, 119.3, 52.1, 41.4, 31.4, 28.7, 19.9; mass spectrum (Cl, NH_3), m/e 140 (MH^+); $[\alpha]_D$ −45.4° (c 1.3, CH_2Cl_2). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41. Found: C, 69.09; H, 9.36.

(5*S*)-(+)-2-Oxopyrrolidine-5-acetic Acid (17). Lactam **15** (24 mg, 0.19 mmol) was dissolved in MeOH (5 mL) and cooled to −78 °C. Ozone was bubbled through the solution for 7 min, the reaction was purged with N_2 for 20 min, NaOH (38 mg, 5 equiv) in 30% H_2O_2 (66 mg, 3 equiv) was added, and the flask was warmed to room temperature. After the mixture was stirred for 22 h, the MeOH was removed in vacuo, and the aqueous residue was extracted twice with CH_2Cl_2. These extracts were discarded. The aqueous layer was acidified with concentrated H_2SO_4 and extracted with CH_2Cl_2 (3×), and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and recrystallized from hexane–EtOAc, affording a solid: 11 mg, 40%; mp 96–98 °C; IR (CH_2Cl_2) 3700–2200 (br), 3300 (m), 1710 (s), 1660 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.90 (br s, 1 H, CO_2H), 7.83 (s, 1 H, NH), 4.08 (m, 1 H, C_5-H), 2.67 (dd, 1 H, J = 17.5, 3.5), 2.52–2.26 (m, 4 H), 1.73 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 175.0, 51.3, 41.0, 29.8, 26.0; mass spectrum (Cl, NH_3), m/e 144 (MH^+); $[\alpha]_D$ +20.3° (c 0.8, EtOH) [lit.[19] $[\alpha]_D$ +17.6° (c 1, EtOH)].

(6*S*)-(+)-2-Oxopiperidine-6-acetic Acid (18). Prepared from lactam **16** (30.1 mg, 0.22 mmol): white solid; 20.7 mg, 61%; mp 129–130 °C; IR (CH_2Cl_2) 3700–2200 (br), 3300 (m), 1720 (s), 1630 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.90 (br s, 1 H, CO_2H), 8.20 (s, 1 H, NH), 3.94 (m, 1 H, C_6-H), 2.65–2.25 (m, 4 H), 2.02–1.70 (m, 3 H), 1.47 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 174.6, 48.6, 40.7, 30.8, 27.3, 18.6; mass spectrum (Cl, isobutane), m/e 158 (MH^+); $[\alpha]_D$ +17.8° (c 1, EtOH) [lit.[12] $[\alpha]_D$ +11.3° (c 1, EtOH)].

(5*R*)-(−)-1-((1*S*)-1-Phenylethyl)-5-propyl-2-pyrrolidinone (19). A mixture of lactam **11a** (56 mg, 0.25 mmol) and HCO_2NH_4 (92 mg, 6 equiv) was dissolved in MeOH (5 mL), 10% Pd/C (20 mg) was added, and the mixture was stirred at 25 °C for 5.5 h. The mixture was filtered, the filtrate was concentrated, and the residue was partitioned between H_2O and CH_2Cl_2. After two further extractions with CH_2Cl_2, the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated, affording a clear oil: 52 mg, 91%; IR (CH_2Cl_2) 1680 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5 H, ArH_5), 5.36 (q, 1 H, J = 7 Hz, ArCH), 3.70 (m, 1 H, C_5-H), 2.48 (m, 1 H, C_3-H_a), 2.32 (ddd, 1 H, J = 17, 9.5, 5, C_3-H_b), 2.09 (m, 1 H, C_4-H), 1.65 (m, 1 H, C_4-H), 1.64 (d, 3 H, J = 7, NCHCH_3Ar), 1.22–0.99 (m, 3 H), 0.94 (m, 1 H, C_7-H), 0.66 (t, 3 H, J = 7, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 142.1, 128.3, 127.2, 127.1, 56.9, 49.5, 36.5, 30.6, 24.5, 18.0, 16.3, 13.8; mass spectrum (Cl, NH_3), m/e 232 (MH^+); $[\alpha]_D$ −135.1° (c 1, CH_2Cl_2). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.93; H, 9.22.

(6*R*)-(−)-1-((1*S*)-1-Phenylethyl)-5-propyl-2-piperidinone (20). Prepared from lactam **13a** (8.9 mg, 0.04 mmol), NH_4HCO_2 (12 mg, 5 equiv), and 10% Pd/C (3 mg) in MeOH (4 mL): clear oil; 7.0 mg, 78%; IR (CH_2Cl_2) 1630 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.22 (m, 5 H, ArH_5), 5.71 (q, 1 H, J = 7, ArCH), 3.40 (m, 1 H, C_6-H), 2.44 (t, 2 H, J = 7.5, C_3-H_2), 1.91–1.58 (m, 4 H), 1.58 (d, 3 H, J = 7, NCHCH_3Ar), 1.26 (m, 1 H), 1.11 (m, 1 H), 0.88 (m, 1 H), 0.72 (m, 1 H), 0.63 (t, 3 H, J = 7, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 141.2, 128.3, 127.9, 127.3, 53.3, 52.7, 34.7, 31.3, 25.9, 19.6, 16.6, 16.1, 13.7; mass spectrum (Cl, NH_3), m/e 246 (MH^+); $[\alpha]_D$ −119.5° (c 1, CH_2Cl_2). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.32; H, 9.50.

(5*S*)-(−)-1-((1*S*)-1-Phenylethyl)-5-propyl-2-pyrrolidinone (21). Prepared from lactam **12a** (11.4 mg, 0.05 mmol), NH_4HCO_2 (19 mg, 6 equiv), and 10% Pd/C (8 mg) in MeOH (4 mL): clear oil; 10.0 mg, 87%; IR (CH_2Cl_2) 1680 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5 H, ArH_5), 5.41 (q, 1 H, J = 7, ArCH), 3.24 (m, 1 H, C_5-H), 2.48 (m, 1 H, C_3-H_a), 2.32 (ddd, 1 H, J = 17, 9.5, 5, C_3-H_b), 1.96 (m, 1 H, C_4-H), 1.70–1.50 (m, 2 H), 1.62 (d, 3 H, J = 7, NCHCH_3Ar), 1.43–1.18 (m, 2 H), 1.08 (m, 1 H), 0.81 (t, 3 H, J = 7, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 139.8, 128.5, 127.5, 127.4, 57.1, 50.6, 37.4, 30.5, 24.3, 18.3, 18.2, 14.0; mass spectrum (Cl, NH_3), m/e 232 (MH^+); $[\alpha]_D$ −0.6° (c 1.2, CH_2Cl_2). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.85; H, 9.17.

(6*S*)-(−)-1-((1*S*)-1-Phenylethyl)-5-propyl-2-piperidinone (22). Prepared from lactam **14a** (13.3 mg, 0.06 mmol), NH_4HCO_2 (21 mg, 6 equiv), and 10% Pd/C (10 mg) in MeOH (4 mL): clear oil; 12 mg, 89%; IR (CH_2Cl_2) 1630 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 5 H, ArH_5), 5.93 (q, 1 H, J = 7, ArCH), 3.07 (m, 1 H, C_6-H), 2.49 (t, 2 H, J = 7, C_3-H_2), 1.86 (m, 1 H), 1.76–1.54 (m, 3 H), 1.60 (d, 3 H, J = 7, NCHCH_3Ar), 1.39–1.02 (m, 4 H), 0.87 (t, 3 H, J = 7, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 140.9, 128.4, 127.5, 127.3, 52.2, 51.9, 36.1, 31.0, 25.4, 19.8, 17.5, 16.1, 14.0; mass spectrum (Cl, NH_3), m/e 246 (MH^+); $[\alpha]_D$ −66.7° (c 0.9, CH_2Cl_2). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.31; H, 9.58.

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Supplementary Material Available: Experimental procedures and characterization data for imides **7a-c**, **8a,b**, hydroxy lactams **9a-c**, **10a,b**, and allyl lactams **11a,b**, **12a-c**, **13a,b**, and **14a,b** (8 pages). Ordering information is given on any current masthead page.

Antiviral and Antitumor Agents from a New Zealand Sponge, *Mycale* sp. 2. Structures and Solution Conformations of Mycalamides A and B

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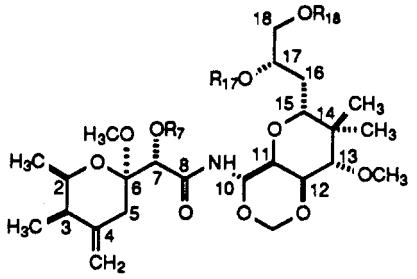
Mycalamide B (2) has been found to occur with mycalamide A (1) in a New Zealand sponge of the genus *Mycale*. Both are potent antiviral and antitumor agents. The solution conformations of mycalamide A (1) have been explored in detail by analysis of ^1H–^1H coupling constants and NOE interactions and modeled by molecular mechanics calculations. Significant populations of several solution conformations were indicated. A comparison of ^1H NMR data showed that analogous conformations were present in solutions of mycalamide B (2) and the structurally similar compounds pederin (4) and onnamide A (6).

The isolation of mycalamide A (1), an antiviral agent from a New Zealand sponge of the genus *Mycale*, has been described recently.[1] This multifunctional heterocyclic compound is also being evaluated as an antitumor agent on the basis of its in vivo activity against P388 murine leukemia and a variety of solid tumor model systems, including Lewis Lung, M5076, Burkitt's Lymphoma, and MX-1 and CX-1 human tumor xenografts.[2] To provide further mycalamide A (1) for this biological testing, more of the active *Mycale* species (family Mycalidae, order Poecilosclerida)[1] was collected and extracted. During this processing a set of ^1H HMR peaks close to those of mycalamide A were noticed in the spectra of some samples. Further chromatography gave a less polar compound, mycalamide B (2), which was also antiviral and had significant in vivo antitumor activity.[2]



1 $R_7 = R_{17} = R_{18} = H$
2 $R_7 = R_{18} = H$, $R_{17} = CH_3$
3 $R_7 = R_{18} = CO.CH_3$, $R_{17} = CH_3$

The ^1H NMR spectrum of mycalamide B was very similar to that of mycalamide A, but contained three, rather than two, methoxyl signals (Table I). High-resolution mass spectroscopy gave a molecular formula $C_{25}H_{43}NO_{10}$ (mycalamide A is $C_{24}H_{41}NO_{10}$), and chemical ionization MS with ND_3 as the reagent gas indicated the presence of just three exchangeable protons,[3] thus implying that one of the three hydroxyl groups of mycalamide A (1) is replaced by a methoxyl group in mycalamide B. The ^{13}C NMR spectrum, assigned by heteronuclear correlation experiments, showed that the greatest difference between A and B was associated with the C17 signal (71.51 ppm in A, 78.84 ppm in B), indicating the presence of the additional methoxyl group at C17.[4] The locations of the two hydroxyl groups of mycalamide B were confirmed by preparing mycalamide B diacetate (3), in which the H7 and H18 NMR signals were each shifted more than 0.6 ppm downfield.

Thus mycalamide B (2) is the 17-methoxyl derivative of mycalamide A (1).[5] To eliminate the possibility that the methoxyl groups in these compounds were solvent-derived, an extraction of the *Mycale* sponge was carried out with ethanol substituted for methanol. This led to the isolation of mycalamides A and B as before. No other compounds in this series have been detected in any extracts of this sponge species.

Mycalamide B (2) was present in the sponge at less than half the level of mycalamide A (1), but it was a more potent antiviral agent in vitro than A (minimum active dose 1–2 ng/disk for B, 3.5–5.0 ng/disk for A[1]). The partially purified extract which had in vivo antiviral activity[1] contained both mycalamides A and B (no in vivo antiviral data have been obtained on the pure compounds). Mycalamide B was more cytotoxic than A (P388 IC_{50}'s 0.7 ± 0.3 and 3.0 ± 1.3 ng/mL, respectively), and B was active in vivo against P388 leukemia at a lower optimum dose than mycalamide A.[2]

The natural products most similar in structure to mycalamides A (1) and B (2) are the insect toxin pederin (4)[6]

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(5) Further work is underway to establish the absolute stereochemistries of C2 to C7, C10 to C15, and C17, which are drawn as for pederin (4) for convenience.
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