Single and Double Diastereoselection in Azomethine Ylide Cycloaddition Reactions with Unsaturated Chiral Bicyclic Lactams†

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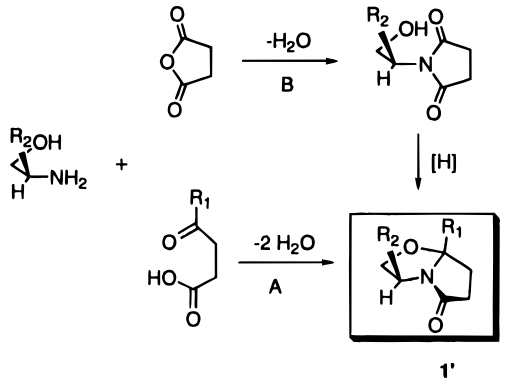
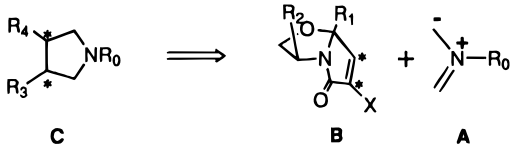
Double diastereoselectivity data were analyzed to provide insight into the structural features that influence π-facial selectivity in 1,3-dipolar cycloadditions of chiral and achiral azomethine ylides to chiral, unsaturated bicyclic lactams. Three major steric contributions to the differences in stability ($\Delta\Delta G^{\ddagger}$) between competing cycloaddition transition states were identified. The first major set of steric interactions involve that between the dipoles and the substituents on the left hemisphere (R_2) and concave faces of the bicyclic lactams. This effectively hindered both α- and β-approaches in the nonextended transition states shown in Figure 1. The second major steric interaction was provided by the nonbonded interactions (i) between the R_1 angular substituent on the bicyclic lactam and the π-system of the dipole as shown in Figures 3 and 4. This interaction was shown to be very significant, causing reversal in π-facial attack of chiral and achiral dipoles when the angular substituent is changed from phenyl or methyl to hydrogen. The high diastereoselectivity observed now opens a route to highly substituted chiral, nonracemic pyrrolidines.

The intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins represents an efficient and convergent method for the construction of the pyrrolidine structural unit.[1,2] Since 1985, interest in the asymmetric synthesis of substituted pyrrolidine derivatives by this process has led to the development of cycloaddition reactions in which chirality resides on one of the two reaction partners. The level of stereoselectivity provided by these bimolecular reactions has been variable and empirically dependent upon the proper combination of chiral dipolarophile[3] or chiral dipole.[4] In contrast, employing a chiral dipole (**A**) *and* a chiral dipolarophile (**B**) for the enhancement of diastereoselection in azomethine ylide cycloadditions has only been demonstrated, to date, by Garner[5,6] and briefly from these laboratories.[7] The former reported excellent diastereofacial selectivity for 1,3-dipolar cycloaddition reactions of a photochemically generated chiral azomethine ylide with a chiral acryloyl sultam.

Scheme 1





We envisaged chiral bicyclic lactams such as **B** to be useful templates for the study of the factors controlling π-facial selectivity since the substituents (R_1, R_2, X) can be systematically varied.[8] Moreover, the regioselective elaboration of the latent ketone (aminal) functionality on **B** would allow for a wide variety of substituents (R_3, R_4) at the 3- and 4-positions of pyrrolidine ring (**C**). In a preliminary study,[7] we described substituent effects that influenced diastereoselectivity in the reaction of chiral, unsaturated bicyclic lactams (**1**) with simple achiral (**2**) and chiral (**3**) azomethine ylides derived from benzylamine and enantiomerically pure (*R*) and (*S*) α-methylbenzylamines, respectively. The levels of single and double diastereoselection[9] in the production of tricyclic lactams **4** and **5** were modest to good (70−88% de);

† Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

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(1) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; A. Padwa, Ed.; Wiley-Interscience: New York, 1984; Vol. 1; p 686.

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(4) For recent results concerning intermolecular 1,3-dipolar cycloaddition of chiral azomethine ylides to achiral dipolarophiles, see Padwa, A.; Chen, Y.-Y.; Chiacchio, U.; Dent, W. *Tetrahedron* **1985**, *41*, 3529. Garner, P.; Sunitha, K.; Ho, W. B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041. Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D.; Wong, L. F. *Tetrahedron: Asymmetry* **1991**, *2*, 1343. Deprez, P.; Rouden, J.; Chiaroni, A.; Riche, C.; Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1991**, *32*, 7531. Deprez, P.; Royer, J.; Husson, H.-P. *Tetrahedron: Asymmetry* **1991**, *2*, 1189. Chastanet, J.; Fathallah, H.; Negron, G.; Roussi, G. *Heterocycles* **1992**, *34*, 1565. Negron, G.; Roussi, G.; Zhang, J. *Heterocycles* **1992**, *34*, 293. Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527.

(5) Garner, P.; Ho, W. B. *J. Org. Chem.* **1990**, *55*, 3973.

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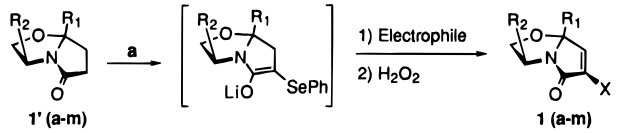
Table 1. Preparation of Dipolarophiles 1a−m from Saturated Bicyclic Lactams 1′a−m

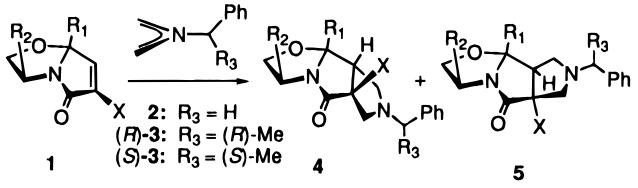


Reagents: (a) i) $LiN(SiMe_3)_2$ (2 eq); ii) PhSeBr (1 eq), THF, -78 °C.

lactam	R_1	R_2	X	electrophile	% yield
1a	Me	*i*-Pr	H	NH_4Cl	82
1b	Me	Ph	H	NH_4Cl	82
1c	H	Ph	H	NH_4Cl	78
1d	Me	*i*-Pr	CO_2Me	$ClCO_2Me$	66
1e	Me	*i*-Pr	CO_2t-Bu	Boc_2O	43
1f	H	Ph	Cl	*p*-$TolSO_2Cl$	71
1g	H	Ph	Br	$(BrCCl_2)_2$	84
1h	H	Ph	I	NIS	55
1i	Me	Ph	Br	$(BrCCl_2)_2$	75
1j	Me	H	H	NH_4Cl	17
1k	Me	*i*-Pr	Me	MeI	77
1l[a]	Me	*t*-Bu	H	NH_4Cl	80
1m	Ph	*i*-Pr	CO_2Me	$ClCO_2Me$	69

[a] This was prepared using LDA (see ref 8).

however, we felt the necessity of increasing the diastereoselection in these cycloaddition processes while gathering additional support for a steric model for the origin of the stereoselectivity. We now report that α−halo-unsaturated bicyclic lactams (**1**, X = halogen) exhibit significantly improved diastereoselection relative to the lactams previously studied (**1** X = H, CO_2R).

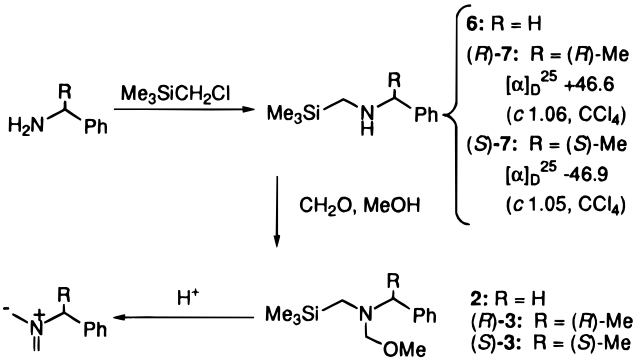


Results and Discussion

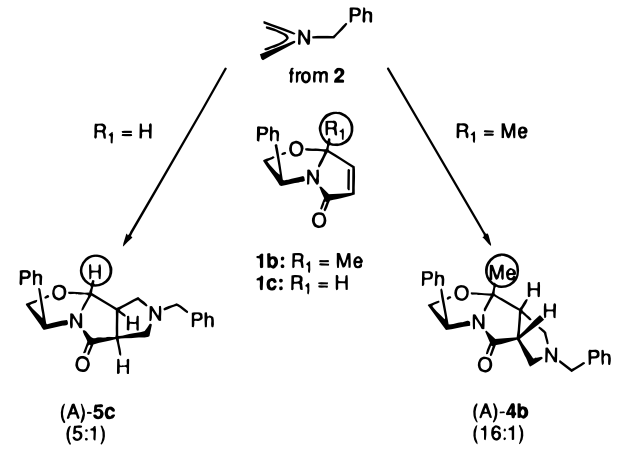
Preparation of Chiral Dipolarophiles. The two general routes to the dipolarophile precursors used in this study are illustrated in Scheme 1. Typically, when the angular substituent (R_1) on bicyclic lactam **1′** was an alkyl or aryl substituent, route A was employed, which involved the cyclocondensation reaction between a chiral amino-alcohol[10] and a keto-acid.[8] Alternatively, route B was used for the preparation of angular hydrogen (R_1 = H) bicyclic lactams **1′**. In this process, condensation of an amino alcohol (R_2 = *i*-Pr, Ph) with succinimide gave an intermediate chiral imide. Partial reduction of the imide to give an intermediate hydroxy lactam, followed by acid-catalyzed ring closure, afforded the desired angular hydrogen bicyclic lactam **1′** (R_1 = H).[11]

Sequential treatment of the saturated lactams **1′** with base (2.0 equiv) followed by the addition of phenylselenenyl bromide (1.0 equiv) gave α-selenenyl enolates that were quenched by a variety of electrophiles. The unsaturated lactams **1a**−**m** were obtained in good yields after oxidation as shown in Table 1. Unsaturated lactams **1g**−**i** were also prepared via a halogenation−dehydrohalogenation sequence in similar yields.[12]

Scheme 2



Scheme 3[a]



(a) The designations (A), (*R*), and (*S*)-**4** or **5** refer to tricyclic derivatives of achiral dipole equivalent **2**, and chiral dipole equivalents (*R*)-**3** and (*S*)-**3**, repectively.

Preparation of Achiral and Chiral Azomethine Ylide Precursors. As shown in Scheme 2, simple achiral (**2**) and chiral (**3**) azomethine ylide precursors were derived from benzylamine and enantiomerically pure (*R*) and (*S*)-α-methylbenzylamines according to Padwa.[13] Thus, alkylation of benzylamine or α-methylbenzylamine (3 equiv) with (chloromethyl)trimethylsilane gave the corresponding secondary amines (**6** or **7**) in 70−80% yields.

Conversion of the latter to the corresponding achiral (**2**) and chiral (**3**) dipole precursors was accomplished by treatment of the appropriate amine with aqueous formaldehyde, followed by the addition of MeOH and solid K_2CO_3 (as water scavenger). Optimum parameters for cycloaddition were achieved by allowing the azomethine precursors **2** or **3** to react with the unsaturated bicyclic lactams utilizing conditions described by Achiwa (catalytic TFA in CH_2Cl_2).[14]

Role of Angular Substituent. Scheme 3 clearly shows that the nature of the substituent (R_1) attached

(10) For a convenient conversion of amino acids to amino alcohols, see McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568 and Varma, R. S.; Kabalka, G. W. *Synth. Comm.* **1985**, 15 (9), 843, and references therein.

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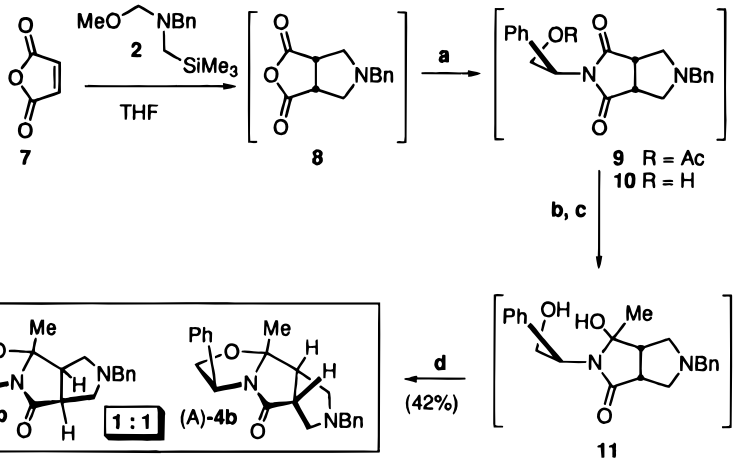
(13) (a) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235. (b) Vedejs, E.; Larson, S.; West, F. G. *J. Org. Chem.* **1985**, *50*, 2171 and earlier references cited.

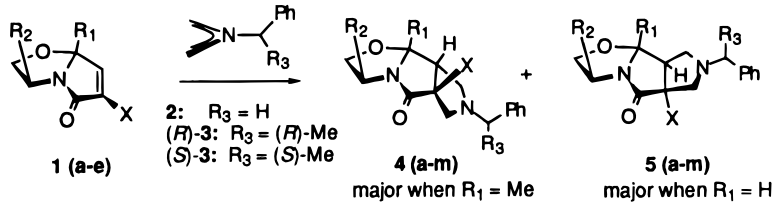
(14) Achiwa, K.; Imai, N.; Motoyama, T.; Sekiya, M. *Chem. Lett.* **1984**, 2041.

Scheme 4[a]



[a] Reagents and Conditions: (a) (i) (*S*)-phenylglycinol (1 equiv), THF, rt, 1 h, (ii) Ac_2O, NaOAc, reflux; (b) 2 N HClEtOH, reflux, 2 h; (c) MeMgBr (3 equiv), THF, rt, 3.3 h; (d) TFA, CH_2Cl_2, rt, 12 h.

Table 2. Effect of Structure on Facial Selectivity



	lactam **1**				ylide **2**	ylide (*R*)-**3**	ylide (*S*)-**3**
entry	R_2	R_1	X	lactam	(A)-**4**:**5**[a]	(*R*)-**4**:**5**[a]	(*S*)-**4**:**5**[a]
1	*i*-Pr	Me	H	**1a**	91:9	94:6	91:9
2	Ph	Me	H	**1b**	94:6	91:9	92:8
3	Ph	H	H	**1c**	17:83	19:81	16:84
4	*i*-Pr	Me	CO_2Me	**1d**	71:29	87:13	59:41
5	*i*-Pr	Me	CO_2t-Bu	**1e**	72:28	92:8	51:49
6	*i*-Pr	Ph	CO_2Me	**1m**	74:26	87:13	69:31

[a] (A)-**4**:**5** refers to adducts derived from the *N*-benzyl (achiral) ylide; (*R*)-**4**:**5** and (*S*)-**4**:**5** refer to adducts from the *R* and *S* α-benzylamine ylides, respectively.

to the angular carbon in **1b** and **1c** determined the overall direction of cycloaddition. Predominant approach of the dipole to the α−face is seen when the angular substituent is large (R_1 = Me) whereas predominant approach to the β-face occurs when the angular substituent is small (R_1 = H). Thus, reaction of 2 equiv of achiral dipole precursor **2** with angular methyl lactam **1b** afforded a 16:1 mixture of cycloadducts (A)-**4b** along with the minor isomer (A)-**5b** in quantitative yield. Stereochemical assignments, made on the basis of ^{13}C NMR, supported the structure of the major isomer (A)-**4b**, arising from predominant approach of the dipole to the "bottom" or α-face of unsaturated lactam **1b**. Crystalline, diastereomerically pure (A)-**4b** was obtained from the crude mix in 56−69% yields. In contrast, reaction of precursor **2** with the angular hydrogen lactam **1c** afforded only a 5:1 mixture of cycloadducts with (A)-**5c** predominating. This is the result of preferential approach of the dipole to the "top" or β-face of **1c**.

With the goal of obtaining sufficient minor isomer (A)-**5b** for unambiguous structural characterization, an alternative synthesis of the tricyclic lactams (A)-**4b** and (A)-**5b** was developed (Scheme 4). In situ cycloaddition of **2** with maleic anhydride (**7**) provided the bicyclic anhydride **8** which was treated with (*S*)-phenylglycinol, followed by acetic anhydride, necessary to produce the crude chiral imide **9**. Hydrolysis of the resulting acetate **9** gave the alcohol **10** in 19% overall yield. Addition of methylmagnesium bromide proceeded nonstereoselectively to provide hydroxy lactams **11**, which were converted to a 1:1 mixture (42%) of tricyclic lactams (A)-**4b** and (A)-**5b** using TFA. Chromatography produced pure (A)-**5b** for structural comparisons.

Role of X-Substituent. Double Diastereoselection. Double asymmetric synthesis[9] of the tricyclic cycloadducts was explored in the hope of obtaining greater levels of diastereoselection in cycloadditions with chiral dipole equivalents (*R*)-**3** and (*S*)-**3**.

Table 2 summarizes the results of the addition to chiral lactams **1a**−**e,m** by achiral **2** and chiral dipoles (*R*)-**3** and (*S*)-**3**. In cases where the α-substituent, X, was hydrogen (entries 1−3), it was observed that the π-facial selectivities were insensitive to the configuration at the benzylic carbon of the dipole. In contrast, where X was larger than hydrogen (entries 4−6, X = CO_2Me or CO_2t-Bu), significantly enhanced selectivity was observed for cycloadditions with the dipole (*R*)-**3**, compared to the ratios provided by the achiral **2** and the dipole (*S*)-**3**.

Transition State Model. Transition state structural insight was derived from the data summarized in Table 2 to allow the construction of a preliminary predictive model for the origin of diastereoselectivity in these 1,3-dipolar cycloadditions. Stereospecificity is well known

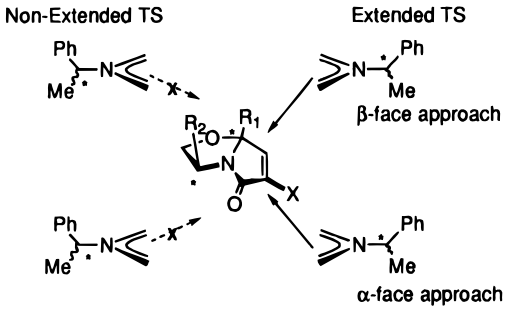
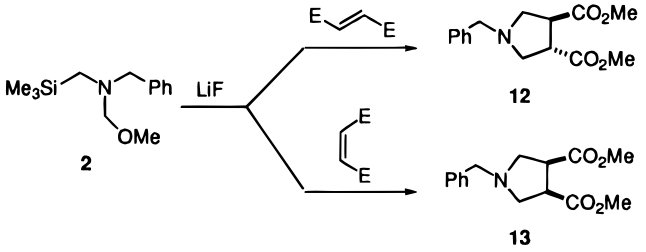


Figure 1. Four competing trajectories of the dipole to the chiral bicyclic lactam.

to be a characteristic of concerted 1,3-dipolar reactions.[15] For example, Padwa[13] has demonstrated that methoxymethylsilylamine **2** adds to dimethyl fumarate and maleate with complete stereospecificity, giving rise to cycloadducts **12** and **13**, respectively.



Starting with the assumption that azomethine ylide cycloadditions to unsaturated bicyclic lactams may occur with concerted bond formation, four competing transition state orientations can be proposed (Figure 1). These orientations allow the π-systems of the two reaction partners to approach each other within two parallel planes.[16]

The trajectories indicated in Figure 1 as *extended* transition orientations are proposed to be more favored than the *nonextended* orientations.[17] As stated earlier, when X = H, the magnitudes of the diastereoselection were insensitive to the configuration at the dipole (Table 2, entries 1−3). This observation is consistent with poor stereochemical "communication" or induction between the sites of asymmetry (*) of the chiral unsaturated lactams and that of the chiral azomethine ylides. The *extended* models are therefore consistent with the maximization of distance between sites of asymmetry and the minimization of nonbonded interactions between dipole and dipolarophile.

Furthermore, since the magnitudes of the diastereoselection was related to the configuration at the dipole when X = CO_2Me or CO_2t-Bu (Table 2, entries 4 and 5), the model was further refined to take this observation into account. Padwa proposed that two Felkin[18] model conformations (**14a** or **14b**) could be adopted by the chiral

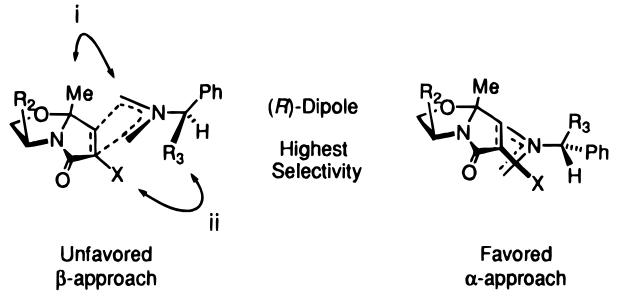
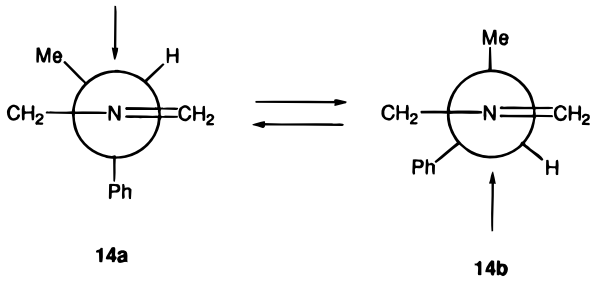


Figure 2. Transition states for reactions of angular methyl bicyclic lactams with (*R*)-**3**.

dipole during the cycloaddition. With regard to reactions of π-systems vicinal to asymmetric centers, Houk[19] has shown that the favored approach of another reacting species is generally *anti* to the largest group perpendicular to the π-system since this trajectory represents the minimum of unfavorable repulsive interactions between vicinal bonds.



Better insight into the nature of the favored conformational preference of the chiral dipole was gained when Newman projections **14a** and **14b** were evaluated with respect to the double diastereoselectivity data collected in Table 2. The observed trends in diastereoselection were best rationalized using transition state models in Figure 2 employing projection **14a**. In this model, approach of the dipolarophile occurs antiperiplanar to the *phenyl* group that is oriented perpendicular to the π-system of the dipole. Consequently, as shown in Table 2 (entries 4 and 5), the intrinsic π-facial selectivity of bicyclic lactams **1d** and **1e** (~40% de, as measured by their reactions with achiral dipole **2**) was due primarily to gauche interactions (i) between the π-system of the dipole and the angular methyl substituent. However, the enhanced selectivity (74−84% de) for α-approach of the dipole derived from (*R*)-**3** to lactams **1d** or **1e** was probably due to increased steric interaction (ii) between substituents X and R_3 in the unfavored transition state for β-approach.

The model in Figure 2 also explains the decreased diastereofacial preferences observed when lactams **1d** or **1e** were allowed to react with (*S*)-**3**. As shown in Figure 3, α-approach is subject to steric interactions (**iii**) between the methyl substituent of the (*S*)-dipole (R_3) and the ester moiety (X = CO_2R) of unsaturated lactams **1d** or **1e**. This interaction would tend to destabilize this transition state relative to that for β-approach and may account for the poor selectivities (2−18% de) observed for this pair of reactants.

(15) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1.

(16) Houk, K. N.; Yamaguchi, K. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2; p 431.

(17) Some ambiguity may be caused by the use of the traditional terms *exo* and *endo* for describing the relative orientations of the dipole and dipolarophile in these cycloaddition transition states. Therefore, regardless of π-facial orientation, the *extended* transition states refer to the cases where the *N*-alkyl substituent on the dipole is directed away from the bulk of the unsaturated bicyclic lactam; whereas the *nonextended* transition states refer to orientations where the substituents of the dipole and bicyclic lactam are disposed toward each other as illustrated in Figure 1.

(18) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199.

(19) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438.

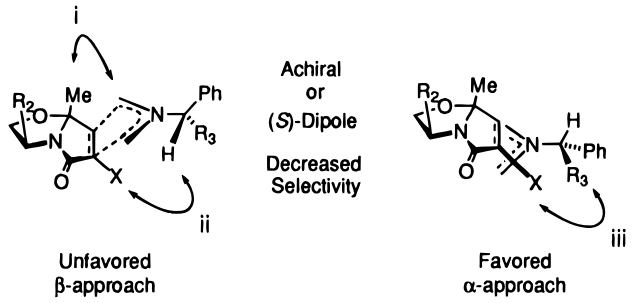


Figure 3. Transition states for reactions of angular methyl bicyclic lactams with **2** (R_3 = H) or (*S*)-**3**.

This model is also consistent with the observation that the magnitude of the diastereoselection observed in 1,3-dipolar reactions with α-unsubstituted lactams **1a**−**c** (X = H) was insensitive to the configuration at the dipole (Table 2, entries 1−3). From the model it follows that interactions ii and iii (cf. Figures 2 and 3) would be minor unless both R_3 and X substituents are larger than hydrogen.

A self-consistent scenario was not obtained when approach of the dipolarophile was assumed to occur antiperiplanar to the *methyl* group oriented perpendicular to the π-system of the dipole (projection **14b**). Apparently, the *phenyl* group is the "large" group with respect to the unique nonbonded interactions encountered in the approach of the chiral dipole to the α-substituted chiral unsaturated bicyclic lactams. This assertion is reasonable when one compares the relative A-values of methyl and phenyl groups (1.74[20] and 2.87[21] kcal/mol, respectively).

α-Halobicyclic Lactams. Based on the above, we next sought to increase the levels of diastereoselection in cycloadditions with angular methyl (R_1 = Me) and angular hydrogen (R_1 = H) bicyclic lactams **1** (cf. Table 2). If the model in Figure 2 is valid, then the intrinsic π-facial selectivities of unsaturated bicyclic lactams should be augmented by increasing steric interaction ii to destabilize the transition state leading to the minor cycloadduct. Since the destabilizing effect of interaction ii would necessarily depend upon the nature of X, we felt that a halogen may fulfill the expected criteria for high selectivity since it is larger than hydrogen and not excessively electron-withdrawing. Concern for synthetic utility also dictated that the halogen be readily removable.

Angular Methyl Lactams 1 (R_1 = Me). According to the model depicted in Figure 2, the use of (*R*)-**3** in cycloaddition reactions with α-halo lactams **1** (R_1 = Me, X = halogen) was expected to afford high selectivity for α-approach of the dipole as a consequence of selective destabilization (ii) of the transition state for β-approach. As shown in Table 3, cycloadduct (*R*)-**4i** was obtained as a single diastereomer when α-bromo lactam **1i** was reacted with (*R*)-**3** (entry 3, matched case); whereas significantly decreased selectivity (82% de) was observed in the reaction of **1i** with (*S*)-**3** (entry 2, mismatched case).

Compared to the reactivity of α-unsubstituted lactam **1b**, the α-bromo lactam **1i** reacted sluggishly with the achiral and chiral azomethine ylides at room temperature, proceeding to only 51−76% conversions after 48 h. However, the use of excess dipole (2−4 equiv) and higher reaction temperature (37 °C) markedly decreased reaction times (2−3 h) and improved the isolated yields of tricyclic product without detectable loss of diastereoselectivity. Presumably, the lower reactivity of **1i** (relative to **1b**) may be attributed to the slow approach of the dipole due to the combined presence of the large bromine atom and the angular methyl group.

Table 3. Effect of Halogen Substituent in Reactions of Angular Methyl Bicyclic Lactams 1b and 1i with Achiral and Chiral Dipoles[a]

entry	lactam	X	dipole	4:5[c]	tricyclic products
1	**1b**	H	(*R*)-**3** or (*S*)-**3** or **2**	~94:6	(*R*),(*S*),(A)[b] **4b,5b**
2	**1i**	Br	(*S*)-**3**	91:9	(*S*)-**4i, 5i**
3	**1i**	Br	(*R*)-**3**	>98:2	(*R*)-**4i**
4	**1i**	Br	**2**	~96:4[d]	(A)-**4i**

[a] Reactions were performed by adding TFA (0.1 equiv) to a solution of dipolarophile (1 equiv, 0.2 M) and dipole precursor (2 equiv) in CH_2Cl_2. [b] For designations (A), (*R*), and (*S*)-**4** or -**5** see footnote in Table 2. [c] The ratios of **4** to **5** were determined by ^{1}H NMR analysis of the crude product mixtures. [d] The crude ratios could not be determined due to complexity of the ^{1}H NMR spectrum. Accordingly, the crude mixture was subjected to reductive dehalogenation ($NaBH_4$, $Ni(OAc)_2$) to give the chromatographically inseparable mixture of (A)-**4b** and (A)-**5b**. This crude mixture was partially purified through a plug of silica gel (1:4 EtOAc/hexanes) to give the ratio 96:4 by ^{1}H NMR analysis.

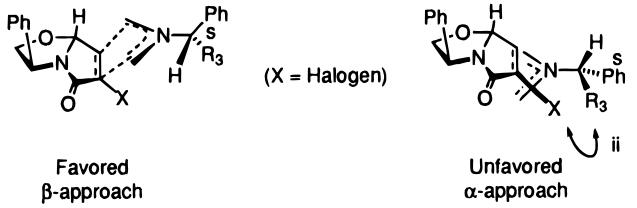


Figure 4. Transition states for reactions of angular hydrogen bicyclic lactams (**1**, X = halogen) with (*S*)-**3**.

Angular Hydrogen Lactams 1 (R_1 = H). In contrast to the reactivity and selectivity of the angular methyl lactams **1** (R_1 = Me), the angular hydrogen lactams **1** (R_1 = H) were found to be more reactive (reactions were typically complete within 1 h) and less selective. For example, the intrinsic diastereofacial selectivity of **1c** (X = H) is moderate (~66% de), favoring the cycloadduct derived from β-approach of the dipole (Table 2, entry 3). In contrast to the model describing the angular methyl lactams (Figure 2), the *(S)-3 dipole equivalent* was predicted to exhibit greater selectivity (Figure 4) for β-approach. This was assumed to be a consequence of greater nonbonded interactions (ii) in the transition state for α-approach.

The results of additions with several angular hydrogen lactams **1c,f**−**h** are summarized in Table 4. As predicted by the model in Figure 4, the (*S*)-dipole produced the highest selectivities when the stereochemical control element X was halogen (entries 2−4). In spite of the increase in halogen size, the diastereoselection observed with (*S*)-**3** was identical, within experimental error (90−94% de). However, the steric effect of the halogens is likely to be attenuated by the increasing halogen polarizabilities and carbon−halogen bond lengths (Cl < Br < I). The fact that these halogens show similar *A* values (0.47−0.53 kcal/mole)[22] makes this a reasonable assumption. The diastereoselectivities observed in reactions

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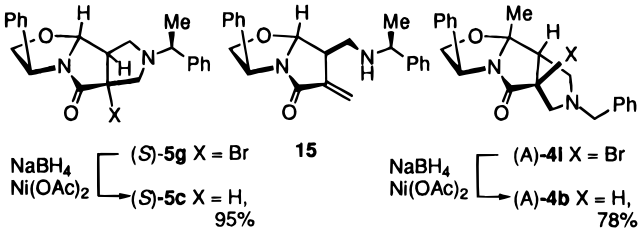
with the achiral dipole **2** (R_3 = H) were insensitive to the nature of X on the bicyclic lactams (Table 4, entries 1−4). This observation is consistent with the expectation that interaction ii (Figure 3) would be minor unless both R_3 and X substituents are larger than hydrogen.

Removal of Halogen Stereocontrol Element. For the sake of synthetic versatility it was necessary to demonstrate that the α-halo substituent could be easily removed. Initial attempts to effect the removal of the halogen from tricyclic lactams (*S*)-**5g** and (A)-**4i** proved to be problematic. For example, reaction of α-bromo tricyclic lactam (*S*)-**5g** with zinc in acetic acid or activated zinc−copper couple[23] gave 64−72% yields of the corresponding dehalogenated product ((*S*)-**5c**) accompanied by 4−14% yields of ring opened product **15**. Lowering the reaction temperature merely decreased the reduction rate without decrease of **15**. Use of samarium diiodide[24,25] under conditions described by Curran[26] and Imamoto[27] gave incomplete reduction of the halogen in **5g**. Incomplete dehalogenation of (*S*)-**5g** was also observed with tributyltin hydride[28] and with magnesium powder.

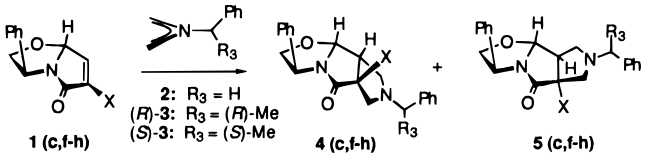
Since transition metals are known to catalyze a number of hydride reductions,[29] the reaction conditions described by Goto and Kishi[30] were explored. Although both (*S*)-**5g** and (A)-**4i** remained essentially unreactive in the presence of excess $NaBH_4$ in MeOH, complete dehalogenation was observed for both halogen adducts within 30 min in the presence of 10% by weight nickel(II) acetate and excess $NaBH_4$ (10 eq.) in yields of 78−95%.



Stereochemical Assignments. The stereochemical assignments for the cycloadducts derived from the angular methyl lactams (**1**, R_1 = Me, Table 1) are based upon difference NOE experiments and ^{13}C NMR chemical shift correlations. For example, 2-D HETCOR experiments on (*R*)-**4d** and (*R*)-**5d** allowed correlations between ^{13}C and ^1H NMR signals that provided unambiguous structural assignment of the methine hydrogen signals corresponding to each isomer.

The results of NOE experiments ($CDCl_3$) on the major ((*R*)-**4d**)) and minor ((*R*)-**5d**)) cycloadducts are shown in Figure 5. The major cycloadduct (*R*)-**4d** is assigned the α−configuration based on the 5.7% enhancement observed for the H methine hydrogen resonance (δ 2.94) when the angular methyl hydrogen resonance at δ 1.55 was irradiated. For the minor isomer, irradiation of the angular methyl hydrogen resonance at δ 1.27 caused a 0.9% enhancement for the methine hydrogen resonance at δ 2.93.

Table 4. Effect of Halogen Substituent in Reactions of Angular Hydrogen Lactams 1c,f−h with Achiral and Chiral Dipoles



entry	X	angular hydrogen lactam	achiral **2**: (A)-**4**:**5**[a]	(*R*)-**3**: (*R*)-**4**:**5**	(*S*)-**3**: (*S*)-**4**:**5**
1	H	**1c**	17:83	19:81	16:84
2	Cl	**1f**	18:82	21:79	**5:95**
3	Br	**1g**	18:82	22:78	**4:96**
4	I	**1h**	18:82	23:77	**3:97**

[a] See footnote on Table 2.

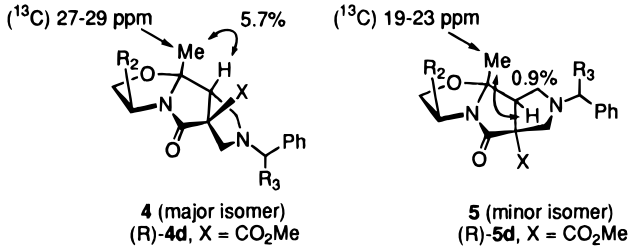


Figure 5.

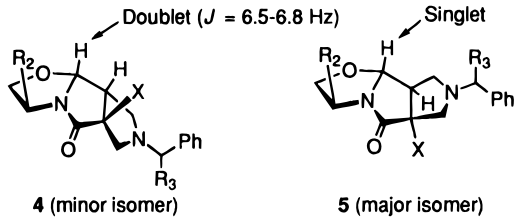


Figure 6.

Significant diagnostic differences in ^{13}C chemical shift existed between the angular methyl signals corresponding to the major (**4**) and minor (**5**) diastereomers. For example, higher shielding was observed for the methyl signal in the minor cycloadducts relative to the corresponding signal in the major cycloadducts. Since the minor cycloadducts **5** exhibited upfield methyl signals (δ 19−23), they were assigned the β-configuration. Similarly, the major tricyclic cycloadducts **4** were assigned the α-configuration since these compounds exhibited downfield angular methyl signals (δ 27−29).

Stereochemical assignments for the angular hydrogen tricyclic lactams **4** and **5c,f−h** are based on the observed magnitude of the coupling (^1H NMR) between the angular H and the adjacent H methine hydrogens corresponding to each isomer (**4** and **5**). As shown in Figure 6, the observation of a singlet (J = 0) for the angular hydrogen of the major isomer is consistent with a ∼90° dihedral angle or *trans* configuration between the two hydrogens.[31]

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(29) For examples of transition metal-catalyzed hydride reductions see: Bosin, T. R.; Raymond, M. G.; Buckpitt, A. R. *Tetrahedron Lett.* **1973**, *47*, 4699; Ashby, E. C.; Lin, J. J. *Tetrahedron Lett.* **1977**, *51*, 4481. Satoh, T.; Mitsuo, N.; Nishiki, M.; Nanba, K.; Suzuki, S. *Chem. Lett.* **1981**, 1029.
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Conclusion

Evidence for a predictive transition state picture describing diastereoselective dipolar cycloadditions of simple azomethine ylides to a structurally variable chiral template has been presented. It is hoped that the steric models presented here would provide insight for the rational control of stereoselection in these processes, especially for the preparation of nonracemic 3,4-disubstituted pyrrolidine-containing building blocks. The latter will be described in a future article.

Experimental Section

***N*-Benzyl-*N*-(methoxymethyl)-*N*-(trimethylsilyl)methylamine (2).** The procedure described by Padwa[32] for the synthesis of *N*-benzyl-*N*-(trimethylsilyl)methylamine (**6**) was followed with the exception that the crude secondary amine was purified by flash chromatography through silica gel (7:1 silica gel/crude) saturated with 5:95 Et_3N/EtOAc. This procedure easily allows the more polar excess benzylamine (R_f 0.14, 5:95 Et_3N/EtOAc) to be separated from the less polar desired secondary amine. Final purification of the secondary amine was accomplished via short-path vacuum distillation through a 15 cm Vigreux column. This method provided pure secondary amine **6** (73%) as a clear colorless liquid: bp 70−71 °C (0.7 mmHg) (lit.[38] bp 89−90 °C (5 mmHg)); R_f 0.59 (5:95 Et_3N/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 5H), 3.79 (s, 2H), 2.04 (s, 2H), 1.10 (br s, 1H), 0.03 (s, 9H).

The procedure described by Padwa for the synthesis of **2**[13] was followed with the exception that **6** (8.4 g, 0.043 mol) was added by syringe dropwise over 45 min to a pH 7, 37% aqueous formaldehyde solution (4.5 mL, 0.065 mol) at 0 °C. Distillation provided **2** as a clear, colorless liquid in 81% yield: bp 77−80 °C (0.1 mmHg) (lit.[13] bp 78−80 °C (5 mmHg)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 3.99 (s, 2H), 3.75 (s, 2H), 3.23 (s, 3H), 2.18 (s, 2H), 0.04 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.7 (s), 128.7 (d), 128.1 (d), 126.8 (d), 88.4 (t), 59.5 (t), 55.4 (q), 42.9 (t), −1.5 (q).

(*R*)-*N*-(1-Phenylethyl)-*N*-(methoxymethyl)-*N*-(trimethylsilyl)methylamine ((*R*)-3). Using the procedure described above for the synthesis of **6**, (*R*)(+)-α-methylbenzylamine (10.4 g, 0.0860 mol) was heated with (chloromethyl)trimethylsilane (3.5 g, 0.029 mol) to provide 3.2 g (94%) of recovered (*R*)(+)-3-methylbenzylamine (R_f 0.25, 5:95 Et_3N/EtOAc) and 5.0 g (84%) of the known[13] secondary amine (*R*)-**7** as a clear, colorless liquid after distillation: bp 64−70 °C (0.5 mmHg), R_f 0.64 (5:95 Et_3N/EtOAc), $[\alpha]^{25}_D$ +46.6 (*c* 1.06, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 3.62 (q, 1H, J = 6.6), 1.87 (ABq, 2H, J = 13.6, $\Delta\nu$ = 21.8), 1.30 (d, 3H, J = 6.4), 1.00 (br s, 1H), 0.01 (s, 9H); IR (film) ν 3083, 1603, 1492 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NSi$: C, 69.49; H, 10.21; N, 6.75. Found: C, 69.76; H, 10.32; N, 6.91.

Using the procedure described above for the synthesis of **2**, (*R*)-**7** (5.42 g, 0.261 mol) was added by syringe dropwise over 45 min to a pH 7, 37% aqueous formaldehyde solution (2.95 mL, 0.0392 mol) at 0 °C. This procedure provided 5.42 g (83%) of (*R*)-**3** as a clear, colorless liquid: bp 82−84 °C (0.2 mmHg), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.11 (ABq, 2H, J = 9.2, $\Delta\nu$ = 59.2), 3.98 (q, 1H, J = 6.7), 3.18 (s, 3H), 2.12 (ABq, 2H, J = 14.6, $\Delta\nu$ = 32.0), 1.36 (d, 3H, J = 6.7), −0.14 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.3 (s), 128.0 (d), 127.5 (d), 126.6 (d), 85.9 (t), 61.8 (d), 54.6 (q), 39.9 (t), 19.2 (q), −1.4 (q); IR (film) ν 3084, 1071 cm^{-1}. Anal. Calcd for $C_{14}H_{25}NOSi$: C, 66.88; H, 10.02; N, 5.57. Found: C, 67.08; H, 10.04; N, 5.75.

(*S*)-*N*-(1-Phenylethyl)-*N*-(methoxymethyl)-*N*-(trimethylsilyl)methylamine ((*S*)-3). Using the procedure described above for the synthesis of (*R*)-**3**, (*S*)(−)-α-methylbenzylamine was converted to secondary amine (*S*)-**7** ($[\alpha]^{25}_D$ −46.9 (*c* 1.05, CCl_4)), which was then converted to (*S*)-**3** ($[\alpha]^{25}_D$ −20.5 (*c* 2.45, CCl_4)).

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General Selenenylation/Oxidation Procedure for the Preparation of Lactams 1. To a −78 °C solution (0.1 M) of bicyclic lactam **1′** (1.0 equiv) in THF was added a 1.0 M solution of $LiN(TMS)_2$ (2.0 equiv) in THF, and the pale yellow solution was allowed to stir 30 min. A 0.3 M THF solution of PhSeBr (1.1 equiv) was added dropwise followed by, after 5 min, the dropwise addition of a 0.3 M THF solution of electrophile (1.1 equiv). After 15 min, a saturated aqueous NH_4Cl solution was added to the −78 °C reaction mixture which was then allowed to warm to rt. The mixture was extracted with Et_2O, and the organic extracts were concentrated under reduced pressure.

To a CH_2Cl_2 solution (∼0.05 M) of the above phenylselenylated products, at 0 °C, was added a 30% H_2O_2 (3 equiv) solution . The resulting heterogeneous mixture was allowed to warm to rt while stirring vigorously for 6 h. The aqueous phase was extracted with CH_2Cl_2, and the organic extracts were combined and washed successively with 1 N HCl and saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford a crude oil which was purified as indicated below.

Unsaturated Bicyclic Lactam 1a. The bicyclic lactam **1a′** (2.0 g, 0.011 mol), derived from (*S*)-valinol and levulinic acid,[33,11] was subjected to the above general selenenylation/oxidation procedure using saturated aqueous NH_4Cl as the electrophile to afford 1.6 g (82%) of **1a** as a pale orange liquid after bulb to bulb vacuum distillation (115 °C, 1.5 mmHg). An analytical sample was prepared by crystallization with hexanes to give white needles: R_f 0.41 (1:1 EtOAc/hexanes); mp 39−42 °C; $[\alpha]^{25}_D$ +48.7 (*c* 1.51, acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, 1H, J = 5.8), 5.98 (d, 1H, J = 5.8), 4.27 (dd, 1H, J = 7.3, 8.9), 4.05 (dd, 1H, J = 5.9, 8.9), 3.48 (ddd, 1H, J = 6.0, 7.3, 10.2), 1.74 (m, 1H), 1.53 (s, 3H), 1.06 (d, 3H, J = 6.7), 0.90 (d, 3H, J = 6.6); IR (film) ν 1716 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34. Found: C, 66.08; H, 8.38.

Unsaturated Bicyclic Lactam 1b. The saturated bicyclic lactam **1b′** was prepared in the following manner. A solution of (*S*)-phenylglycinol (3.52 g, 0.0257 mol) and levulinic acid (2.98 g, 0.0257 mol) in toluene (100 mL) was heated at reflux and stirred overnight with azeotropic removal of water. Toluene was removed under reduced pressure, and the resulting solids were recrystallized from hot EtOAc/hexanes. This process yielded 4.55 g (82%) of the saturated bicyclic lactam **1b′** as yellow-white needles: mp 127−129 °C, R_f 0.25 (1:1 EtOAc/hexanes), $[\alpha]^{25}_D$ +147 (*c* 1.08, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.15 (t, 1H, J = 7.5), 4.59 (app t, 1H, J = 8.5), 4.08 (dd, 1H, J = 7.0, 8.8), 2.86 (dt, 1H, J = 9.8, 17.2), 2.57 (ddd, 1H, J = 5.2, 7.6, 12.8), 2.27 (m, 2H), 1.43 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.9 (s), 140.0 (s), 128.6 (d), 127.4 (d), 125.5 (d), 100.4 (s), 73.2 (t), 57.6 (d), 33.8 (t), 33.1 (t), 24.2 (q); IR (film) ν 1721 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.95; H, 7.01; N, 6.44.

Bicyclic lactam **1b′** (2.35 g, 0.0108 mol) was subjected to the general selenenylation/oxidation procedure using saturated aqueous NH_4Cl as the electrophile. This procedure afforded 1.62 g (70%) of **1b** as a pale yellow powder after flash chromatography: R_f 0.43 (1:1 EtOAc/hexanes); mp 83−85 °C; $[\alpha]^{25}_D$ +114 (*c* 1.54, acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 7.10 (d, 1H, J = 5.6), 6.08 (d, 1H, J = 5.8), 5.06 (app t, 1H, J = 7.0), 4.66 (app t, 1H, J = 8.5), 4.30 (dd, 1H, J = 6.4, 8.8), 1.53 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.9 (s), 151.0 (d), 139.7 (s), 128.7 (d), 128.0 (d), 127.5 (d), 125.8 (d), 101.0 (s), 75.9 (t), 58.3 (d), 21.8 (q); IR (film) ν 1720 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.27; H, 6.07.

Unsaturated Bicyclic Lactam 1c. The bicyclic lactam **1c′** (106 mg, 0.522mmol), derived from (*S*)-phenylglycinol and succinic anhydride,[11] was subjected to the above general selenenylation/oxidation procedure using saturated aqueous NH_4Cl as the electrophile. This procedure afforded 81.6 mg (78%) of **1c** as a white powder after radial chromatography: R_f 0.46 (1:1 benzene/Et_2O); mp 74−75 °C; $[\alpha]^{25}_D$ +116 (*c* 1.55, acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 7.20 (dd, 1H, J = 1.5, 5.9), 6.22 (d, 1H, J = 5.9), 5.65 (d, 1H, J = 0.8), 4.96 (app t, 1H, J = 7.2), 4.73 (dd, 1H, J = 7.4, 8.8), 4.07 (dd,

1H, $J = 7.3, 8.8$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.7 (s), 145.6 (d), 139.3 (s), 131.5 (d), 128.8 (d), 127.7 (d), 126.0 (d), 93.9 (d), 78.3 (t), 57.9 (d); IR (film) ν 1716 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51. Found: C, 71.59; H, 5.53.

Unsaturated Bicyclic Lactam 1d. Bicyclic lactam **1a′** (506 mg, 2.76 mmol), derived from (*S*)-valinol and levulinic acid,[33,11] was subjected to the above general selenenylation/oxidation procedure using methyl chloroformate as the electrophile to afford unsaturated lactam **1d**[34] in 66% yield.

Unsaturated Bicyclic Lactam 1e. Bicyclic lactam **1a′** (1.0 g, 5.5 mmol), derived from (*S*)-valinol and levulinic acid,[33,11] was subjected to the above general selenenylation/oxidation procedure using di-*tert*-butyl dicarbonate as the electrophile to afford unsaturated lactam **1e**[34] in 43% yield.

Unsaturated Bicyclic Lactam 1f. Bicyclic lactam **1c′** (103 mg, 0.507mmol), derived from (*S*)-phenylglycinol and succinic anhydride,[11] was subjected to the above general selenenylation/oxidation procedure using *p*-toluenesulfonyl chloride (102 mg, 0.535 mmol) as the electrophile. This procedure afforded 84.3 mg (71%) of **1f** as a tan powder after radial chromatography: R_f 0.63 (Et_2O); mp 84−89 °C; $[\alpha]^{25}_D$ +161 (*c* 0.99, acetone); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 7.11 (d, 1H, $J = 1.8$), 5.60 (d, 1H, $J = 1.9$), 5.00 (app t, 1H, $J = 7.4$), 4.77 (dd, 1H, $J = 7.5, 9.0$), 4.07 (dd, 1H, $J = 7.4, 8.9$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.3 (s), 138.5 (s), 137.8 (d), 134.9 (s), 128.9 (d), 127.9 (d), 126.0 (d), 90.8 (d), 77.9 (t), 58.5 (d); IR (film) ν 1725, 1604 cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28. Found: C, 61.02; H, 4.20.

Unsaturated Bicyclic Lactam 1g. Bicyclic lactam **1c′** (202 mg, 0.994mmol), derived from (*S*)-phenylglycinol and succinic anhydride,[11] was subjected to the above general selenenylation/oxidation procedure using 1,2-dibromotetrachloroethane (358 mg, 1.09 mmol) as the electrophile. This procedure afforded 233 mg (84%) of **1g** as a pale yellow powder after radial chromatography: R_f 0.31 (1:4 EtOAc/hexanes); mp 101−104 °C; $[\alpha]^{25}_D$ +154 (*c* 1.57, acetone); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.38 (m, 6H), 5.57 (d, 1H, $J = 1.8$), 5.00 (app t, 1H, $J = 7.3$), 4.75 (dd, 1H, $J = 7.4, 9.0$), 4.07 (dd, 1H, $J = 7.3, 9.0$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8 (s), 142.6 (d), 138.5 (s), 128.8 (d), 127.9 (d), 125.9 (d), 124.8 (s), 92.3 (d), 77.8 (t), 58.5 (d); IR (film) ν 3081, 1713, 1679, 1641 cm^{-1}. Anal. Calcd for $C_{12}H_{10}BrNO_2$: C, 51.45; H, 3.60. Found: C, 51.40; H, 3.64.

Unsaturated Bicyclic Lactam 1h. Bicyclic lactam **1c′** (102 mg, 0.499 mmol), derived from (*S*)-phenylglycinol and succinic anhydride,[11] was subjected to the above general selenenylation/oxidation procedure using *N*-iodosuccimide (124 mg, 0.549 mmol) as the electrophile. This procedure afforded 89.0 mg (55%) of **1h** as a pale yellow powder after radial chromatography: R_f 0.65 (Et_2O); mp 74−76 °C; $[\alpha]^{25}_D$ +147 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, 1H, $J = 1.8$), 7.25−7.40 (m, 5H), 5.58 (d, 1H, $J = 1.7$), 5.02 (app t, 1H, $J = 7.2$), 4.73 (dd, 1H, $J = 7.4, 8.9$), 4.09 (dd, 1H, $J = 7.1, 8.9$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.5 (s), 150.9 (d), 138.7 (s), 128.8 (d), 127.8 (d), 125.9 (d), 100.2 (s), 94.5 (d), 77.8 (t), 58.6 (d); IR (film) ν 1706 cm^{-1}. Anal. Calcd for $C_{12}H_{10}INO_2$: C, 44.04; H, 3.09; N, 4.28. Found: C, 44.18; H, 3.04; N, 4.23.

Unsaturated Bicyclic Lactam 1i. Bicyclic lactam **1b′** (200 mg, 0.921 mmol), derived from (*S*)-phenylglycinol and levulinic acid (see preparation for **1b**), was subjected to the general selenenylation/oxidation procedure using 1,2-dibromotetrachloroethane (329 mg, 1.01 mmol) as the electrophile. This procedure afforded 204 mg (75%) of **1i** as a white solid after radial chromatography: R_f 0.66 (Et_2O); mp 98−101 °C; $[\alpha]^{25}_D$ +130 (*c* 1.55, acetone); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.39 (m, 5H), 7.23 (s, 1H), 5.11 (app t, 1H, $J = 7.1$), 4.68 (dd, 1H, $J = 7.9, 8.9$), 4.29 (dd, 1H, $J = 6.5, 9.0$), 1.53 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.1 (s), 148.0 (d), 139.0 (s), 128.8 (d), 127.7 (d), 125.7 (d), 121.5 (s), 99.8 (s), 75.7 (t), 59.0 (d), 21.9 (q); IR (film) ν 1715 cm^{-1}. Anal. Calcd for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76. Found: C, 53.16; H, 4.15; N, 4.70.

Unsaturated Bicyclic Lactam (±)-1j. A solution of ethanolamine (4.2 g, 0.069 mol), ethyl levulinate (9.9 g, 0.069 mol), and K_2CO_3 (2 g) in toluene (50 mL) was heated at reflux for 36 h. The mixture was diluted with CH_2Cl_2 and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure, and the resulting liquid was vacuum distilled (71−73 °C, 1 mmHg) to afford 3.86 g (40%) of (±)-**1j′** as clear, colorless liquid. For the known[35,36] racemic saturated bicyclic lactam ((±)-**1j′**) (7a*RS*)-5-oxo-7a-methyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole: R_f 0.14 (1:1 EtOAc/hexanes); bp 71−73 °C, 1 torr; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (m, 3H), 3.13 (m, 1H), 2.68 (m, 1H), 2.45 (m, 1H), 2.16 (m, 2H), 1.40 (s, 3H).

Bicyclic lactam (±)-**1j′** (113 mg, 0.800 mmol) was subjected to the general selenenylation/oxidation procedure using saturated aqueous NH_4Cl as the electrophile. This procedure afforded 19.4 mg (17%) of (±)-**1j** as a pale yellow oil after partial purification via radial chromatography (1:1 EtOAc/hexanes): R_f 0.47 (EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, 1H, $J = 5.8$), 5.99 (d, 1H, $J = 5.7$), 4.13 (m, 1H), 3.91 (m, 2H), 3.24 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.6 (s), 151.3 (d), 127.7 (d), 99.9 (s), 69.5 (t), 42.5 (t), 22.2 (q).

Unsaturated Bicyclic Lactam 1k. Bicyclic lactam **1a′** (500 mg, 2.73 mmol), derived from (*S*)-valinol and levulinic acid,[33,11] was subjected to the above general selenenylation/oxidation procedure using methyl iodide as the electrophile to afford the known[8] unsaturated lactam **1k** in 77% yield.

Unsaturated Bicyclic Lactam 1m. Bicyclic lactam **1m′** (500 mg, 2.03 mmoles), derived from (*S*)-valinol and 3-benzoylpropionic acid,[37] was subjected to the above general selenenylation/oxidation procedure using methyl chloroformate as the electrophile to afford unsaturated lactam **1m** as a very light yellow powder in 69% yield: R_f 0.40 (4:5 Et_2O/hexanes); mp 77−79 °C; $[\alpha]_D = +197$ (*c* 1.01, acetone); ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.49 (m, 2H), 7.36 (m, 3H), 4.47 (dd, 1H, $J = 7.4, 8.8$), 3.81 (t, 1H, $J = 8.1$), 3.81 (s, 3H), 3.62 (dt, 1H, $J = 7.4, 10.3$), 1.31 (m, 1H), 1.05 (d, 3H, $J = 6.6$), 0.71 (d, 3H, $J = 6.6$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.5 (s), 161.5 (s), 155.5 (d), 136.0 (s), 129.3 (d), 129.2 (d), 128.9 (d), 126.0 (d), 99.6 (s), 75.3 (t), 62.5 (d), 52.3 (q), 32.3 (d), 20.7 (q), 18.8 (q); IR (film) ν 1766, 1737, 1635 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_4$ C, 67.76; H, 6.36. Found: C, 67.71; H, 6.34.

Azomethine Ylide Cycloadditions to Unsaturated Bicyclic Lactams. General Procedure. Using the conditions of Achiwa,[38] a 0.2 M CH_2Cl_2 solution of a mixture of unsaturated bicyclic lactam (1.0 equiv) and dipole precursor **2**, **(*R*)-3**, or (*S*)-**3** (2.0−4.0 equiv) was treated with trifluoroacetic acid (0.1 equiv). After complete consumption of starting lactam was indicated by TLC, the mixture was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product mixture was analyzed by ^1H NMR to determine the diastereomeric ratios. Purification was then accomplished via column, radial, or preparative thin-layer chromatography.

Cycloadducts (A)-4a and (A)-5a. Using the above general procedure, a 0 °C solution of lactam **1a** (50.0 mg, 0.276 mmol) and **2** (134 mg, 0.552 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.21 mL, 0.028 mmol) and was immediately allowed to warm to rt with stirring for 2.7 h. Integration of the resolved signals corresponding to the major isomer ((A)-**4a**: δ 1.02, 1.45) and the minor isomer ((A)-**5a**: δ 1.07, 1.35) indicated a ratio of 91:9. Column chromatography (1:9 to 1:1 EtOAc/hexanes) of the crude mixture afforded 86.7 mg (99.9%) of an inseparable mixture of (A)-**4a** and (A)-**5a** as a clear, colorless syrup.

For (A)-**4a**: R_f 0.46 (EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 4.08 (dd, 1H, $J = 7.3, 8.0$), 3.87 (dd, 1H, $J = 4.8, 8.3$), 3.66 (m, 1H), 3.52 (ABq, 2H, $J = 13.3$, $\Delta\nu = 49.2$), 3.23 (m, 2H), 3.09 (dd, 1H, $J = 3.0, 9.6$), 2.69 (td, 1H, $J = 3.1, 8.4$),

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2.34 (dd, 1H, J = 6.7, 9.1), 2.20 (dd, 1H, J = 5.1, 9.0), 1.69 (m, 1H), 1.44 (s, 3H), 1.02 (d, 3H, J = 6.7), 0.89 (d, 3H, J = 6.6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.0 (s), 138.8 (s), 128.3 (d), 128.2 (d), 126.8 (d), 98.3 (s), 71.4 (t), 62.1 (d), 59.1 (t), 57.0 (t), 54.1 (t), 49.8 (d), 47.6 (d), 32.7 (d), 28.2 (q), 20.2 (q), 19.3 (q); IR (film) for a 91:9 mixture of (A)-**4a** and (A)-**5a**: ν 1709 cm^{-1}. Anal. for a 91:9 mixture of (A)-**4a** and (A)-**5a**; calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.44; H, 8.40; N, 9.00. GCMS (70 ev) for a 91:9 mixture of (A)-**4a** and (A)-**5a**; for (A)-**4a**: t_R 11.9 min; 314 (100 M$^+$), 284 (62), 269 (15), 223 (58), 158 (29), 128 (8), 91 (85), 42 (48); for (A)-**5a**: t_R 12.1 min; 314 (100 M$^+$), 284 (15), 269 (5), 223 (31), 158 (19), 128 (25), 91 (39), 42 (14).

Cycloadducts (*S*)-4a and (*S*)-5a. Employing the above general procedure, a 0 °C solution of lactam **1a** (46.7 mg, 0.258 mmol) and (*S*)-**3** (162 mg, 0.645 mmol) in CH_2Cl_2 was treated with TFA (1 drop) and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((*S*)-**4a**: δ 1.03, 0.90) and the minor isomer ((*S*)-**5a**: δ 1.06, 0.87) indicated a ratio of 91:9. Radial chromatography (1:1 EtOAc/hexanes) of the crude mixture afforded 84.6 mg (93.1%) of an inseparable mixture of (*S*)-**4a** and (*S*)-**5a** as a clear, colorless oil. For (*S*)-**4a**: R_f 0.59 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.07 (app t, 1H, J = 8.1), 3.85 (dd, 1H, J = 4.9, 7.8), 3.68 (m, 1H), 3.40 (d, 1H, J = 8.9), 3.23 (app t, 1H, J = 7.7), 3.10 (q, 1H, J = 6.7), 2.93 (dd, 1H, J = 2.5, 9.7), 2.62 (td, 1H, J = 2.4, 8.4), 2.26 (app t, 1H, J = 7), 2.07 (m, 1H), 1.68 (m, 1H), 1.41 (s, 3H), 1.30 (d, 3H, J = 6.4), 1.03 (d, 3H, J = 6.5), 0.90 (d, 3H, J = 6.6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.3 (s), 145.4 (s), 128.2 (d), 127.4 (d), 126.9 (d), 98.4 (s), 71.4 (t), 64.5 (d), 62.0 (d), 55.3 (t), 53.5 (t), 49.6 (d), 47.2 (d), 32.8 (d), 28.3 (q), 23.3 (q), 20.3 (q), 19.3 (q); IR (film) of a 91:9 mixture of (*S*)-**4a** and (*S*)-**5a**: ν 1711, 1601 cm^{-1}. Anal. of a 91:9 mixture of (*S*)-**4a** and (*S*)-**5a**; Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59. Found: C, 72.96; H, 8.64. GCMS (70 ev) of a 91:9 mixture of (*S*)-**4a** and (*S*)-**5a**; for (*S*)-**4a**: t_R 12.1 min, 328 (22, M$^+$), 314 (23), 313 (100), 251 (4), 223 (4), 178 (5), 158 (3), 137 (2), 110 (3), 105 (15), 103 (4), 94 (2), 91 (4), 79 (5), 77 (5), 68 (5), 43 (15), 41 (12); for (*S*)-**5a**: t_R 12.3 min, 328 (14, M$^+$), 314 (22), 313 (100), 251 (8), 223 (3), 158 (2), 137 (2), 105 (10), 91 (2), 79 (4), 77 (3), 43 (6), 41 (7).

Cycloadducts (A)-4b and (A)-5b. Using the above general procedure, a 0 °C solution of lactam **1b** (500 mg, 2.32 mmol) and **2** (1.10 g, 4.65 mmol) in CH_2Cl_2 (12 mL) was treated with neat TFA (17.7 mL, 0.23 mmol) and was immediately allowed to warm to rt with stirring for 7.5 h. Integration of the resolved signals corresponding to the major isomer ((A)-**4b**: δ 1.40) and the minor isomer ((A)-**5b**: δ 1.24) indicated a ratio of 93.7:6.3. Column chromatography (1:4 to 100:0 EtOAc/hexanes) of the crude mixture afforded 800 mg (99%) of a mixture of (A)-**4b** and (A)-**5b** as a clear, colorless syrup.

Column chromatography (1:50 MeOH/CH_2Cl_2) of an aliquot of the 88% de mixture afforded essentially pure (A)-**4b** (98.6% de) as a white crystalline solid. For (A)-**4b**: R_f 0.54 (5:95 MeOH/CH_2Cl_2). For (A)-**5b**: R_f 0.67 (5:95 MeOH/CH_2Cl_2). Pure (A)-**4b** could be obtained directly from the crude product mixture in 56−69% yields by using the following procedure. The crude product mixture, obtained by the reaction of **1b** (1.60 g, 7.43 mmol), **2** (3.52 g, 14.8 mmol), and TFA (57 mL, 0.74 mmol) in CH_2Cl_2 (20 mL), was diluted with 1:4 Et_2O/hexanes and cooled to −78 °C under a blanket of argon. A pure seed crystal of (A)-**4b** was added and the mixture was allowed to warm to rt while scratching the sides of the flask with a glass rod. Crystallization occurred and the collected solids were triturated with cool 1:4 Et_2O/hexanes to give 1.78 g (69%) of pure (A)-**4b** as a white powder.

For (A)-**4b:** mp 58−60 °C; R_f 0.32 (1:1 EtOAc/hexanes); $[\alpha]^{25}_D$ +120 (c 1.02, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H); 5.24 (app t, 1H, J = 6.7); 4.54 (app t, 1H, J = 7.9); 4.19 (dd, 1H, J = 5.9, 8.5); 3.58 (ABq, 2H, J = 13.3, $\Delta\nu$ = 50.8); 3.38 (ddd, 1H, J = 1.4, 6.9, 8.3); 3.30 (app d, 1H, J = 9.4); 3.21 (dd, 1H, J = 3.0, 9.7); 2.80 (app td, 1H, J = 3.0, 8.3); 2.41 (dd, 1H, J = 6.9, 9.0); 2.26 (app t, 1H, J = 9.1); 1.40 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.1 (s), 139.9 (s), 138.8 (s), 128.5 (d), 128.3 (d), 128.2 (d), 127.4 (d), 126.9 (d), 125.8 (d), 98.9 (s), 73.1 (t), 59.0 (t), 57.8 (d), 56.9 (t), 54.0 (t), 50.0 (d), 47.4 (d), 27.3 (q); IR (film) ν 3086, 3061, 3028, 2974, 1712, 1604 cm^{-1}. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.80; H, 6.98; N, 8.00. GCMS (70 eV) of a 93.5:6.5 mixture of (A)-**4b** and (A)-**5b**: One peak, t_R 13.8 min; 348 (21 M$^+$), 229 (6.7), 227 (33.6), 158 (36.2), 91 (100), 77 (8.9), 65 (19), 42 (24). For (A)-**5b:** R_f 0.53 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.24 (app t, 1H, J = 7.7), 4.58 (app t, 1H, J = 8.5), 3.99 (dd, 1H, J = 6.9, 8.4), 3.61 (ABq, 2H, J = 12.9, $\Delta\nu$ = 79.8), 3.33 (d, 1H, J = 9.5), 3.22 (app t, 1H, J = 9.5), 3.05 (d, 1H, J = 10.3), 2.87 (dd, 1H, J = 6.7, 9.3), 2.39 (app t, 1H, J = 9.2), 2.16 (dd, 1H, J = 6.7, 10.3), 1.24 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 182.5 (s), 140.8 (s), 138.7 (s), 128.6 (d), 128.5 (d), 128.3 (d), 127.22 (d), 127.15 (d), 125.3 (d), 102.1 (s), 71.4 (t), 59.2 (t), 58.8 (d), 57.2 (t), 55.5 (t), 48.6 (d), 46.1 (d), 19.2 (q).

Alternative Synthesis of (A)-4b and 5b from 10. To a rt solution of imide **10** (138 mg, 0.394 mmol) in THF (3 mL) was added a 3.0 M solution of methylmagnesium bromide in Et_2O (0.39 mL, 1.18 mmoles) dropwise. The clear, brown solution was allowed to stir at rt for 3.3 h. TLC analysis (EtOAc) revealed complete consumption of starting material. The mixture was quenched with saturated, aqueous NH_4Cl and was extracted into Et_2O. The organic extracts were dried ($MgSO_4$) and concentrated to afford the crude mixture of intermediate hydroxy lactams **11** (R_f 0.33 and 0.10, EtOAc). Hydroxy lactam mixture **11** was diluted with CH_2Cl_2 (20 mL), treated with TFA (0.10 mL, 1.3 mmoles), and allowed to stir for 18 h at rt. The resulting clear, yellow solution was poured into a solution of saturated, aqueous $NaHCO_3$, and the aqueous layer was washed thoroughly with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to afford a yellow oil that was partially purified by radial chromatography (1:1 EtOAc/hexanes). The first lot corresponded to pure (A)-**5b** (5 mg, R_f 0.53, EtOAc), and the second lot corresponded to a ∼1:1 mixture of (A)-**5b** and (A)-**4b** (52.7 mg, R_f 0.53 and R_f 0.48, EtOAc) to afford a yield of 42% for the tricyclic lactams derived from imide **10**.

Reductive Dehalogenation of (A)-4i To Give (A)-4b. To a 0 °C suspension of bromotricycle (A)-**4i** (45.6 mg, 0.107 mmol) and $Ni(OAc)_2{\cdot}4H_2O$ (4.5 mg, 0.018 mmol) in MeOH (2 mL) was added $NaBH_4$ (40 mg, 1.1 mmoles) in one portion, forming a dark brown mixture with vigorous gas evolution. The mixture was allowed to warm immediately to rt and was stirred for 33 min. The reaction mixture was partitioned between saturated Na_2EDTA (10 mL) and Et_2O (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), and the ethereal extracts were combined, dried (Na_2SO_4), and concentrated to afford white solids. Dilution with CH_2Cl_2 gave a gellike insoluble material which was filtered through a plug of $MgSO_4$ and concentrated. Radial chromatographic purification of the residue (1:1 EtOAc/hexanes) afforded 29.2 mg (78.3%) of an inseparable mixture of (A)-**4b** and (A)-**5b** as a clear, colorless oil. Integration of the resolved signals corresponding to the major isomer ((A)-**4b**: δ 1.40 (s, 3H)) and the minor isomer ((A)-**5b**: δ 1.25 (s, 3H) indicated a ratio of 96.0:4.0.

Cycloadducts (*R*)-4b and (*R*)-5b. Using the above general procedure, a 0 °C solution of lactam **1b** (20.6 mg, 0.0957 mmol) and (*R*)-**3** (50.4 mg, 0.200 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.013 mmol) and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((*R*)-**4b**: δ 3.07, 4.59) and the minor isomer ((*R*)-**5b**: δ 3.99) indicated a ratio of 92.0:8.0. No further characterization data was obtained.

Cycloadducts (*S*)-4b and (*S*)-5b. Using the above general procedure, a 0 °C solution of lactam **1b** (21.8 mg, 0.101 mmol) and (*S*)-**3** (53.9 mg, 0.214 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.013 mmol) and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((*S*)-**4b**: δ 2.73, 3.47) and the minor isomer ((*S*)-**5b**: δ 4.60) indicated a ratio of 91.1:8.9. Radial chromatography (1:4 EtOAc/hexanes) of the crude mixture gave 26.8 mg (73%) of an inseparable mixture of (*S*)-**4b** and (*S*)-**5b** as a clear, colorless film.

For (*S*)-**4b:** R_f 0.58 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.26 (app t, 1H, J = 8.0), 4.52 (app t, 1H, J = 8.2), 4.18 (dd, 1H, J = 5.8, 8.4), 3.45 (d, 1H, J = 9.1), 3.37 (m, 1H), 3.15 (m, 1H), 3.03 (dd, 1H, J = 2.9, 9.9), 2.73 (m, 1H), 2.33 (m, 1H), 2.14 (m, 1H), 1.36 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$ one accidental degeneracy present.) δ 180.4 (s), 145.3 (s), 140.0 (s), 128.6 (d), 128.2 (d), 127.4 (d), 126.9 (d), 125.8 (d), 98.9 (s), 73.1 (t), 64.5 (d), 57.8 (d), 55.3 (t), 53.4 (t), 49.8 (d), 47.1 (d), 27.3 (q), 23.4 (q); IR (film) of a 91:9 mixture of (*S*)-**4b** and (*S*)-**5b**: ν 3027, 2973, 2789, 1711, 1602, 1493, 1029, 700 cm^{-1}. For (*S*)-**5b**, selected ^{1}H NMR signals: δ 4.60 (app t, 1H, J = 8.5), 4.02 (dd, 1H, J = 6.9, 8.4), 3.26 (q, 1H, J = 6.6), 2.89 (dd, 1H, J = 5.8, 8.6), 2.24 (m, 1H); GCMS (70 eV) of a 91:9 mixture of (*S*)-**4b** and (*S*)-**5b**: one peak, t_R 17.1 min; 362 (13 M$^+$), 347 (55), 285 (6), 257 (7), 200 (7), 173 (5), 158 (45), 131 (27), 130 (20), 105 (100), 103 (30), 91 (38), 90 (23), 77 (42), 68 (10).

Cycloadducts (A)-4c and (A)-5c. Using the above general procedure, a 0 °C solution of lactam **1c** (74.9 mg, 0.372 mmol) and **2** (177 mg, 0.744 mmol) in CH_2Cl_2 was treated with neat TFA (3 mL, 0.04 mmol) and was immediately allowed to warm to rt with stirring for 12 h. Integration of the resolved signals corresponding to the major isomer ((A)-**5c**: δ 4.90 (s, 1H)) and the minor isomer ((A)-**4c**: δ 5.36 (d, 1H, J = 6.8)) indicated a ratio of 83:17. Column chromatography (1:9 to 1:1 EtOAc/hexanes) of the crude mixture afforded 118 mg (95%) of an inseparable mixture of (A)-**5c** and (A)-**4c** as a pale yellow-white solid. Trituration of this mixture with 1:1 Et_2O/hexanes gave 46.7 mg of a white solid which was enriched significantly (93:7) in (A)-**5c**.

For (A)-**5c:** mp 77−83 °C; R_f 0.33 (Et_2O); $[\alpha]^{25}_D$ +41 (*c* 0.97, CCl_4 for 87% de); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.45 (m, 10H), 5.12 (app t, 1H, J = 7.4), 4.90 (s, 1H), 4.55 (app t, 1H, J = 8.2), 3.74 (app t, 1H, J = 7.3), 3.65 (ABq, 2H, J = 13.2, $\Delta\nu$ = 39.0), 3.19 (m, 2H), 2.97 (d, 1H, J = 9.6), 2.85 (app t, 1H, J = 7.0), 2.40 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$ one accidental degeneracy present in aryl region) δ 181.0 (s), 139.8 (s), 138.6 (s), 128.8 (d), 128.3 (d), 127.6 (d), 127.1 (d), 125.7 (d), 99.0 (d), 74.2 (t), 58.5 (t), 58.0 (t), 58.0 (d), 56.7 (t), 48.6 (d), 42.1 (d); IR (film) ν 3061, 3028, 2958, 1711, 1604 cm^{-1}. Anal. for a 93.5:6.5 mixture of (A)-**5c** and (A)-**4c**; calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.35; H, 6.65; N, 8.35.

Cycloadducts (*R*)-4c and (*R*)-5c. Using the above general procedure, a 0 °C solution of lactam **1c** (23.0 mg, 0.114 mmol) and (*R*)-**3** (48.0 mg, 0.191 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.011 mmol) and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((*R*)-**5c**: δ 4.80 (s, 1H) and the minor isomer ((*R*)-**4c**: δ 5.40 (d, 1H, J = 6.8)) indicated a ratio of 81.4:18.6. No further characterization data was obtained.

Cycloadducts (*S*)-4c and (*S*)-5c. Using the above general procedure, a 0 °C solution of lactam **1c** (22.3 mg, 0.111 mmol), and (*S*)-**3** (53.7 mg, 0.214 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.011 mmol) and was immediately allowed to warm to rt with stirring for 12 h. Integration of the resolved signals corresponding to the major isomer ((*S*)-**5c**: δ 4.97 (s, 1H) and the minor isomer ((*S*)-**4c**: δ 5.33 (d, 1H, J = 6.8)) indicated a ratio of 84.2:15.8.

For (*S*)-**5c:** R_f 0.35 (1:1 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.12 (app t, 1H, J = 7.4), 4.97 (s, 1H), 4.57 (app t, 1H, J = 8.3), 3.77 (dd, 1H, J = 7.2, 8.6), 3.32 (q, 1H, J = 6.6), 3.12 (m, 2H), 2.96 (app d, 1H, J = 9.7), 2.87 (app t, 1H, J = 6.7), 2.43 (dd, 1H, J = 6.6, 9.3), 2.33 (app t, 1H, J = 9.1), 1.39 (d, 3H, J = 6.6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.1 (s), 144.7 (s), 139.9 (s), 128.8 (d), 128.4 (d), 127.5 (d), 127.0 (d), 126.8 (d), 125.6 (d), 99.1 (d), 74.2 (t), 63.4 (d), 57.8 (d), 56.1 (t), 55.6 (t), 48.3 (d), 42.0 (d), 22.8 (q); IR (film) for a 97:3 mixture of (*S*)-**5c** and (*S*)-**4c**: ν 3061, 3029, 1713, 1603, 1065, 1029 cm^{-1}. Anal. for a 97:3 mixture of (*S*)-**5c** and (*S*)-**4c**; calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94. Found: C, 75.80; H, 6.91.

Reductive Dehalogenation of (*S*)-5g To Give (*S*)-5c. To a 0 °C suspension of bromotricycle (*S*)-**5g** (44.3 mg, 0.104 mmol) and $Ni(OAc)_2 \cdot 4H_2O$ (4.3 mg, 0.017 mmol) in MeOH (2 mL) was added $NaBH_4$ (45 mg, 1.2 mmol) in one portion, forming a dark brown mixture with vigorous gas evolution. The mixture was allowed to warm immediately to rt and was stirred for 1 h. The reaction mixture was partitioned between saturated Na_2EDTA (10 mL) and Et_2O (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), and the ethereal extracts were combined, dried (Na_2SO_4), and concentrated to a residue. Dilution with CH_2Cl_2 gave a gellike insoluble material which was filtered through a plug of $MgSO_4$ and concentrated to afford 34.5 mg (95%) of (*S*)-**5c** as a white semisolid that was judged greater than 95% pure by ^{1}H NMR.

Cycloadducts (A)-4d and (A)-5d. Using the above general procedure, a 0 °C solution of lactam **1d** (22.0 mg, 0.0919 mmol) and **2** (33 mg, 0.139 mmol) in CH_2Cl_2 was treated with a 0.09 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.009 mmol) and was immediately allowed to warm to rt with stirring for 2 h. Integration of the resolved signals corresponding to the major isomer ((A)-**4d**: δ 1.03, 1.52, 2.53) and the minor isomer ((A)-**5d**: δ 1.08, 1.37, 2.75) indicated a ratio of 71.1:28.9. Column chromatography (1:9 to 1:1 Et_2O/hexanes) of the crude mixture afforded 31.5 mg (92%) of a mixture of (A)-**4d** and (A)-**5d** as a clear, colorless film. Additional prep-TLC (1:1 EtOAc/hexanes) of the mixture gave 19.1 mg of (A)-**4d** and 8.9 mg of (A)-**5d**, both as clear, colorless films.

For (A)-**4d:** R_f 0.11 (1:1 Et_2O/hexanes); $[\alpha]^{25}_D$ 38.3 (*c* 1.68, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 5H); 4.11 (dd, 1H, J = 7.1, 8.3); 3.88 (dd, 1H, J = 4.9, 8.4); 3.73 (s, 3H); 3.69 (ddd, 1H, J = 5.0, 7.1, 11.0); 3.50 (ABq, 2H, J = 13.3, $\Delta\nu$ = 35.3); 3.49 (d, 1H, J = 9.1); 3.27 (app d, 1H, J = 9.7); 2.91 (dd, 1H, J = 1.9, 8.4); 2.52 (d, 1H, J = 9.1); 2.22 (app t, 1H, J = 9.0); 1.71 (m, 1H); 1.51 (s, 3H); 1.02 (d, 3H, J = 6.7), 0.89 (d, 3H, J = 6.6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.2 (s), 170.0 (s), 138.3 (s), 128.3 (d), 128.2 (d), 127.0 (d), 97.7 (s), 71.5 (t), 66.6 (s), 62.5 (d), 60.6 (t), 58.8 (t), 54.4 (t), 52.8 (q), 52.1 (d), 32.7 (d), 27.8 (q), 20.2 (q), 19.2 (q); IR (film) ν 2961, 2874, 2800, 1741, 1714, 1495 cm^{-1}. Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.82; H, 7.63; N, 7.58.

For (A)-**5d:** R_f 0.07 (1:1 Et_2O/hexanes); $[\alpha]^{25}_D$ −13.6 (*c* 1.07, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 5H); 4.21 (app t, 1H, J = 8.0); 3.71 (s, 3H); 3.43−3.79 (m, 4H); 3.38 (d, 1H, J = 9.8); 3.01 (m, 2H); 2.75 (d, 1H, J = 9.9); 2.20 (dd, 1H, J = 6.6, 10.4); 1.68 (m, 1H); 1.36 (s, 3H); 1.07 (d, 3H, J = 6.6); 0.86 (d, 3H, J = 6.6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.2 (s), 170.8 (s), 138.4 (s), 128.5 (d), 128.3 (d), 127.2 (d), 100.3 (s), 77.2 (s), 69.9 (t), 64.5 (d), 60.0 (t), 59.0 (t), 55.1 (t), 53.0 (q), 51.6 (d), 34.2 (d), 20.9 (q), 19.8 (q), 19.0 (q); IR (neat) ν 2959, 2873, 1741, 1711, 1453 cm^{-1}.

Cycloadducts (*R*)-4d and (*R*)-5d. Using the above general procedure, a 0 °C solution of lactam **1d** (102.7 mg, 0.429 mmol) and (*R*)-**3** (162 mg, 0.644 mmol) in CH_2Cl_2 was treated with TFA (4 μL) and was immediately allowed to warm to rt with stirring for 3.0 h. Integration of the resolved signals corresponding to the major isomer ((*R*)-**4d**: δ 0.93, 1.03) and the minor isomer ((*R*.)-**5d**: δ 1.11) indicated an average ratio of 86.8:13.2. Column chromatography (1:1 Et_2O/hexanes) purification of the crude mixture afforded 155 mg (93.4%) of a mixture of (*R*)-**4d** and (*R*)-**5d** as a clear, colorless film.

For (*R*)-**4d:** R_f 0.56 (1:1 EtOAc/hexanes); $[\alpha]^{25}_D$ +52.2 (*c* 1.64, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 5H), 4.18 (dd, 1H, J = 6.8, 8.1), 3.96 (dd, 1H, J = 4.3, 8.2), 3.73 (m, 1H), 3.69 (s, 3H), 3.48 (app d, 1H, J = 9.5), 3.28 (d, 1H, J = 9.3), 3.15 (q, 1H, J = 6.6), 2.94 (dd, 1H, J = 2.1, 8.5), 2.36 (d, 1H, J = 9.3), 2.27 (app t, 1H, J = 9.0), 1.75 (m, 1H), 1.55 (s, 3H), 1.27 (d, 3H, J = 6.6), 1.03 (d, 3H, J = 6.7), 0.93 (d, 3H, J = 6.6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.0 (s), 170.0 (s), 144.5 (s), 128.4 (d), 127.0 (d), 126.8 (d), 97.8 (s), 71.5 (t), 66.2 (s), 64.0 (d), 62.7 (d), 59.4 (t), 52.8 (q), 52.8 (t), 52.0 (d), 32.3 (d), 28.1 (q), 22.9 (q), 20.1 (q), 19.3 (q); IR (film) ν 3084, 3065, 2970, 1738, 1715, 1601 cm^{-1}. Anal. for a 86.6:13.5 mixture of (*R*)-4d and (*R*)-5d; Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.43; H, 7.83; N, 7.28.

For (*R*)-**5d**: R_f 0.48 (1:1 EtOAc/hexanes); $[\alpha]^{25}_D$ −15.5 (*c* 1.13, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.19 (app t, 1H, J = 8.0), 3.72 (s, 3H), 3.72 (d, 1H, J = 15.3), 3.66 (m, 1H), 3.60 (d, 1H, J = 9.9), 3.17 (q, 1H, J = 6.5), 2.93 (d, 1H, J = 15.3), 2.75 (d, 2H, J = 9.7), 2.05 (dd, 1H, J = 6.8, 10.6), 1.70 (m, 1H), 1.34 (d, 3H, J = 6.5), 1.27 (s, 3H), 1.11 (d, 3H, J =

6.6), 0.87 (d, 3H, $J = 6.6$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.6 (s), 170.9 (s), 144.9 (s), 128.4 (d), 127.2 (d), 126.9 (d), 100.4 (s), 69.8 (t), 64.9 (d), 64.6 (d), 64.4 (s), 58.3 (t), 54.7 (t), 53.0 (q), 51.2 (d), 34.1 (d), 22.7 (q), 21.0 (q), 19.7 (q), 18.9 (q); IR (film) ν 2962, 1742, 1712, 1453 cm^{-1}. Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82. Found: C, 68.38; H, 7.87.

Cycloadducts (*S*)-4d and (*S*)-5d): Using the above general procedure, a 0 °C solution of lactam **1d** (49.6 mg, 0.207 mmol), and **(*S*)-3** (79.8 mg, 0.317 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.14 mL, 0.018 mmol) and was immediately allowed to warm to rt with stirring for 2.5 h. Integration of the resolved signals corresponding to the major isomer ((*S*)-**4d**: δ 2.49, 1.29) and the minor isomer ((*S*)-**5d**: δ 2.56, 1.34) indicated a ratio of 59.3:40.7. Prep-TLC (1:1 Et_2O/hexanes) purification of the crude mixture afforded 73.6 mg (92%) of a mixture of (*S*)-**4d** and (*S*)-**5d** as a clear, colorless film. Additional prep-TLC of the mixture gave 36 mg of (*S*)-**4d** and 28.6 mg of (*S*)-**5d**, both as clear, colorless films.

For (*S*)-**4d:** R_f 0.28 (1:1 Et_2O/hexanes); $[\alpha]^{25}_D$ 29.6 (*c* 1.25, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 5H); 4.12 (dd, 1H, $J = 7.2, 8.3$); 3.86 (dd, 1H, $J = 5.1, 8.3$); 3.75 (s, 3H); 3.70 (m, 2H); 3.10 (m, 2H); 2.83 (dd, 1H, $J = 1.7, 8.5$); 2.49 (d, 1H, $J = 8.9$); 2.07 (app t, 1H, $J = 8.9$); 1.68 (m, 1H); 1.47 (s, 3H); 1.28 (d, 3H, $J = 6.6$); 1.03 (d, 3H, $J = 6.7$); 0.90 (d, 3H, $J = 6.6$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.3 (s), 170.1 (s), 144.8 (s), 128.1 (d), 127.0 (d), 126.9 (d), 97.7 (s), 71.4 (t), 66.5 (s), 64.1 (t), 62.3 (d), 58.8 (t), 53.8 (t), 52.8 (q), 51.6 (d), 32.9 (d), 27.6 (q), 23.0 (q), 20.3 (q), 19.2 (q); IR (film) ν 3062, 3027, 2970, 1743, 1715, 1602 cm^{-1}.

For (*S*)-**5d:** R_f 0.16 (1:1 Et_2O/hexanes); $[\alpha]^{25}_D$ −39.4 (*c* 1.19, CCl_4) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 5H), 4.22 (app t, 1H, $J = 8.4$), 3.77 (dd, 1H, $J = 6.9, 8.6$), 3.67 (s, 3H), 3.61 (ddd, 1H, $J = 7.1, 10.9, 14.7$), 3.35 (d, 1H, $J = 10.2$), 3.25 (q, 1H, $J = 6.5$), 3.07 (m, 2H), 2.56 (d, 1H, $J = 10.1$), 2.26 (dd, 1H, $J = 6.4, 10.1$), 1.69 (m, 1H), 1.55 (s, 3H), 1.34 (d, 3H,$J = 6.5$), 1.06 (d, 3H, $J = 6.6$), 0.87 (d, 3H, $J = 6.5$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.1(s), 170.8 (s), 144.6 (s), 128.5 (d), 127.1 (d), 126.7 (d), 100.3 (s), 69.9 (t), 64.2 (d), 64.1 (s), 63.7 (d), 59.0 (t), 53.0 (t), 52.9 (q), 51.3 (d), 34.2 (d), 22.8 (q), 20.9 (q), 19.7 (q), 19.0 (q); IR (film) ν 3061, 3028, 2965, 1745, 1713, 1668, 1602 cm^{-1}. Anal. Calcd for $C_{22}H_{30}N_2O_4$ C, 68.37; H, 7.82; N, 7.25. Found: C, 68.15; H, 7.85; N, 7.17.

Cycloadducts (A)-4e and (A)-5e. Using the above general procedure, a 0 °C solution of lactam **1e** (50.0 mg, 0.178 mmol) and **2** (63.2 mg, 0.266 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.14 mL, 0.018 mmol) and was immediately allowed to warm to rt with stirring for 3.4 h. Integration of the resolved signals corresponding to the major isomer ((A)-**4e**: δ 1.45) and the minor isomer ((A)-**5e**: δ 1.41) indicated a ratio of 72.1:27.9. Column chromatography (1:9 to 1:1 Et_2O/ hexanes) of the crude mixture afforded 37.1 mg (50%) of an inseparable mixture of (A)-**4e** and (A)-**5e** as a clear, colorless film.

For (A)-**4e**, selected ^{1}H NMR signals: δ 4.12 (dd, 1H, $J = 7.2, 8.2$), 3.27 (d, 1H, $J = 9.7$), 2.57 (d, 1H, $J = 9.2$), 1.80 (d, 3H, $J = 6.6$), 1.52 (s, 3H), 1.45 (s, 9H), 1.08 (d, 3H, $J = 6.6$), 0.90 (d, 3H, $J = 6.6$). For (A)-**5e**, selected ^{1}H NMR signals: δ 4.18 (app t, 1H, $J = 8.2$), 3.33 (d, 1H, $J = 9.9$), 2.71 (d, 1H, $J = 9.8$), 1.41 (s, 9H), 1.34 (s, 3H), 1.08 (d, 3H, $J = 6.6$), 1.03 (d, $J = 6.7$), 0.87 (d, 3H, $J = 6.5$). Anal. for a 72.1:27.9 mixture of (A)-**4e** and (A)-**5e**; calcd for $C_{24}H_{34}N_2O_4$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.37; H, 8.32; N, 6.76.

Cycloadducts (*R*)-4e and (*R*)-5e. Using the above general procedure, a 0 °C solution of lactam **1e** (50.0 mg, 0.178 mmol) and (*R*)-**3** (67.1 mg, 0.267 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.14 mL, 0.018 mmol) and was immediately allowed to warm to rt with stirring for 3.5 h. Integration of the resolved signals corresponding to the major isomer ((*R*)-**4e**: δ 3.42, 0.92) and the minor isomer ((*R*)-**5e**: δ 3.53 (d, 1H, $J = 9.6$), 1.12 (d, 3H, $J = 6.6$)) indicated a ratio of 91.6:8.4. Column chromatography (1:5 Et_2O/ hexanes) of the crude mixture afforded 71.5 mg (94%) of an inseparable mixture of (*R*)-**4e** and (*R*)-**5e** as a clear, colorless syrup.

For (*R*)-**4e:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 5H), 4.17 (dd, 1H, $J = 8.1, 6.9$), 3.94 (dd, 1H, $J = 4.3, 8.2$), 3.72 (m, 1H), 3.42 (dd, 1H, $J = 2.1, 9.5$), 3.18 (d, 1H, $J = 9.4$), 3.15 (q, 1H, $J = 6.5$), 2.80 (dd, 1H, $J = 2.3, 8.5$), 2.42 (d, 1H, $J = 9.3$), 2.28 (app t, 1H, $J = 9$), 1.73 (m, 1H), 1.54 (s, 3H), 1.14 (s, 9H), 1.26 (d, 3H, $J = 6.6$), 1.03 (d, 3H, $J = 6.7$), 0.92 (d, 3H, $J = 6.6$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.6 (s), 168.9 (s), 144.8 (s), 128.3 (d), 126.9 (d), 126.8 (d), 97.7 (s), 82.2 (s) 71.6 (t), 67.1 (s), 64.0 (d), 62.3 (d), 58.9 (t), 52.8 (t), 52.7 (d), 32.5 (d), 27.9 (q), 22.9 (q), 20.0 (q), 19.3 (q), 18.4 (q); IR (film) ν 3062, 2972, 1738, 1732, 1714, 1602 cm^{-1}.

Cycloadducts (*S*)-4e and (*S*)-5e. Using the above general procedure, a 0 °C solution of lactam **1e** (50.0 mg, 0.178 mmol) and (*S*)-**3** (67.1 mg, 0.267 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.14 mL, 0.018 mmol) and was immediately allowed to warm to rt with stirring for 3.5 h. Integration of the resolved signals corresponding the isomers (*S*)-**4e** and (*S*)-**5e** indicated a ratio of 51:49. Column chromatography (1:5 Et_2O/hexanes) of the crude mixture afforded 64.3 mg (84.5%) of an inseparable mixture of (*S*)-**4e** and (*S*)-**5e** as a clear, colorless syrup.

For a 1:1 mixture of (*S*)-**4e** and (*S*)-**5e**, selected resolved ^{1}H NMR signals: δ 4.20 (app t, 1H, $J = 8.2$), 4.13 (app t, 1H, $J = 7.8$), 2.11 (app t, 1H, $J = 10.1$), 2.05 app t, 1H, $J = 14.6$), 1.46 (s, 9H), 1.38 (s, 9H), 1.33 (d, 3H, $J = 6.6$), 1.28 (d, 3H, $J = 6.6$), 1.07 (d, 3H, $J = 6.7$), 1.04 (d, 3H, $J = 6.7$), 0.91 (d, 3H, $J = 6.6$), 0.88 (d, 3H, $J = 6.6$).

Cycloadducts (A)-4f and (A)-5f. Using the above general procedure, a 0 °C solution of lactam **1f** (21.8 mg, 0.0925 mmol) and **2** (44.9 mg, 0.189 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.011 mmol) and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((A)-**5f**: δ 4.82 (s, 1H) and the minor isomer ((A)-**4f**: δ 5.48 (d, 1H, $J = 6.7$)) indicated a ratio of 81.9:18.1. No further characterization data was obtained.

Cycloadducts (*R*)-4f and (*R*)-5f. Using the above general procedure, a 0 °C solution of lactam **1f** (22.3 mg, 0.0946 mmol) and (*R*)-**3** (48.7 mg, 0.194 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.011 mmol) and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((*R*)-**5f**: δ 4.72 (s, 1H) and the minor isomer ((*R*)-**4f**: δ 5.52 (d, 1H, $J = 6.6$)) indicated a ratio of 79.0:21.0. No further characterization data was obtained.

Cycloadducts (*S*)-4f and (*S*)-5f. Using the above general procedure, a 0 °C solution of lactam **1f** (23.4 mg, 0.0993 mmol), and (*S*)-**3** (51.7 mg, 0.206 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.013 mmol) and was immediately allowed to warm to rt with stirring for 12 h. Integration of the resolved signals corresponding to the major isomer ((*S*)-**5f**: δ 4.90 (d, 1H, $J = 0.83$)) and the minor isomer ((*S*)-**4f**: δ 5.44 (d, 1H, $J = 6.6$)) indicated a ratio of 95.2:4.8. Radial chromatography (1:4 EtOAc/hexanes) of the crude mixture afforded 33.5 mg (88%) of an inseparable mixture of (*S*)-**5f** and (*S*)-**4f** as a white powder.

For (*S*)-**5f:** R_f 0.35 (1:4 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.21 (app t, 1H, $J = 7.4$), 4.90 (s, 1H), 4.63 (app t, 1H, $J = 8.3$), 3.82 (app t, 1H, $J = 8.1$), 3.42 (m, 2H), 3.32 (app d, 1H, $J = 9.4$), 2.99 (app d, 1H, $J = 5.7$), 2.74 (dd, 1H, $J = 6.0, 9.4$), 2.50 (app d, 1H, $J = 10.3$), 1.39 (d, 3H, $J = 6.4$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.2 (s), 143.8 (s), 139.2 (s), 129.0 (d), 128.6 (d), 127.8 (d), 127.4 (d), 126.7 (d), 125.6 (d), 96.0 (d), 74.2 (t), 72.2 (s), 65.2 (t), 62.7 (d), 58.5 (d), 54.6 (t), 53.0 (d), 22.2 (q); IR (film) ν 3063, 3026, 1727, 1641, 1604 cm^{-1}.

Cycloadducts (A)-4g and (A)-5g. Using the above general procedure, a 0 °C solution of lactam **1g** (21.8 mg, 0.0778 mmol) and **2** (39.0 mg, 0.164 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.011 mmol) and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((A)-**5g**: δ 4.86 (s, 1H) and the minor isomer ((A)-**4g**: δ 5.49 (d, 1H, $J = 6.6$)) indicated a ratio of 82.0:18.0. No further characterization data was obtained.

Cycloadducts (*R*)-4g and (*R*)-5g. Using the above general procedure, a 0 °C solution of lactam **1g** (23.1 mg, 0.0825 mmol) and (*R*)-**3** (35.2 mg, 0.140 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.011 mmol)

and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((*R*)-**5g**: δ 4.76 (s, 1H) and the minor isomer ((*R*)-**4g**: δ 5.53 (d, 1H, J = 6.6)) indicated a ratio of 78.1:21.9. No further characterization data was obtained.

Cycloadducts (*S*)-4g and (*S*)-5g. Using the above general procedure, a 0 °C solution of lactam **1g** (24.1 mg, 0.0860 mmol) and (*S*)-**3** (34.2 mg, 0.136 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.013 mmol) and was immediately allowed to warm to rt with stirring for 17 h. Integration of the resolved signals corresponding to the major isomer ((*S*)-**5g**: δ 4.94 (s, 1H)) and the minor isomer ((*S*)-**4g**: δ 5.44 (d, 1H, J = 6.5)) indicated a ratio of 96.2:3.7. Radial chromatography (1:4 EtOAc/hexanes) of the crude mixture afforded 33.1 mg (90%) of an inseparable mixture of (*S*)-**5g** and (*S*)-**4g** as a white powder.

For (*S*)-**5g:** R_f 0.39 (1:4 EtOAc/hexanes); mp 168−174 °C (91.2% d.e); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H); 5.21 (app t, 1H, J = 7.3); 4.93 (s, 1H); 4.62 (dd, 1H, J = 7.8, 8.5); 3.83 (dd, 1H, J = 6.8, 8.6); 3.42 (m, 2H); 3.19 (d, 1H, J = 9.5), 3.12 (d, 1H, J = 6.3); 2.73 (dd, 1H, J = 6.3, 9.4); 2.64 (d, 1H, J = 10.3); 1.38 (d, 3H, J = 6 .6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.6 (s), 143.7 (s), 139.3 (s), 129.0 (d), 128.6 (d), 127.8 (d), 127.4 (d), 126.7 (d), 125.6 (d), 96.5 (d), 74.1 (t), 65.6 (t), 62.7 (d), 61.9 (s), 58.8 (d), 54.8 (t), 53.2 (d), 22.2 (q); IR (film) for a 95.6:4.4 mixture of (*S*)-**5g** and (*S*)-**4g**: ν 3025, 2971, 2930, 1723, 1603 cm^{-1}. Anal. for a 95.6:4.4 mixture of (*S*)-**5g** and (*S*)-**4g**; calcd for $C_{22}H_{23}BrN_2O_2$ C, 61.83; H, 5.43; N, 6.56. Found: C, 61.86; H, 5.46; N, 6.47.

Cycloadducts (A)-5h and (A)-4h. Using the above general procedure, a 0 °C solution of lactam **1h** (23.4 mg, 0.0715 mmol) and **2** (34.8 mg, 0.147 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.011 mmol) and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((A)-**5h**: δ 4.93 (s, 1H) and the minor isomer ((A)-**4h**: δ 5.49 (d, 1H, J = 6.6)) indicated a ratio of 82.1:17.9. No further characterization data was obtained.

Cycloadducts (*R*)-5h and (*R*)-4h. Using the above general procedure, a 0 °C solution of lactam **1h** (17.4 mg, 0.0532 mmol) and (*R*)-**3** (27.2 mg, 0.108 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.011 mmol) and was immediately allowed to warm to rt with stirring for 24 h. Integration of the resolved signals corresponding to the major isomer ((*R*)-**5h**: δ 4.82 (s, 1H) and the minor isomer ((*R*)-**4h**: δ 5.52 (d, 1H, J = 6.5)) indicated a ratio of 77.3:22.7. No further characterization data was obtained.

Cycloadducts (*S*)-5h and (*S*)-4h. Using the above general procedure, a 0 °C solution of lactam **1h** (19.6 mg, 0.0599 mmol), and (*S*)-**3** (36.5 mg, 0.145 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.013 mmol) and was immediately allowed to warm to rt with stirring for 12 h. Integration of the resolved signals corresponding to the major isomer ((*S*)-**5h**: δ 5.01 (s, 1H)) and the minor isomer ((*S*)-**4h**: δ 5.44 (d, 1H, J = 6.7)) indicated a ratio of 96.6:3.4. Radial chromatography (1:4 EtOAc/hexanes) of the crude mixture afforded 23.0 mg (81%) of an inseparable mixture of (*S*)-**5h** and (*S*)-**4h** as a pale yellow semisolid.

For (*S*)-**5h:** R_f 0.30 (1:4 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.19 (app t, 1H, J = 7.2), 5.00 (s, 1H), 4.59 (app t, 1H, J = 8.0), 3.82 (dd, 1H, J = 6.7, 8.2), 3.40 (m, 2H), 3.22 (app d, 1H, J = 6.7), 3.11 (app d, 1H, J = 9.6), 2.74 (app d, 1H, J = 9.4), 2.69 (partially obscured dd, 1H, J = 6.8, 9.4), 1.37 (d, 3H, J = 6.6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.6 (s), 143.8 (s), 139.5 (s), 129.0 (d), 128.6 (d), 127.8 (d), 127.3 (d), 126.7 (d), 125.7 (d), 97.3 (d), 73.9 (t), 67.9 (t), 62.5 (d), 59.2 (d), 55.2 (t), 54.5 (d), 37.4 (s), 22.3 (q); IR (film) for a 97:3 mixture of (*S*)-**5h** and (*S*)-**4h**: ν 3060, 3029, 1718, 1604 cm^{-1}.

Cycloadduct (A)-4i. To a rt solution of **1i** (51.0 mg, 0.173 mmol) and **2** (85 mg, 0.36 mmol) in CH_2Cl_2 (2.5 mL) was added TFA (1 drop). The resulting solution was heated to 37 °C and was stirred for 2 h. The reaction mixture was quenched with excess saturated, aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the organic extracts were dried (Na_2SO_4) and concentrated. The crude residue was purified by radial chromatography (5:95 Et_2O/CH_2Cl_2) to give 62.6 mg (84.5%) of (A)-**4i** as a colorless film: R_f 0.37 (5:95 Et_2O/CH_2Cl_2); $[\alpha]^{25}_D$ +92.6 (*c* Et_2O/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.4 (m, 10), 4.54 (dd, 1H, J = 7.7, 8.6), 4.22 (dd, 1H, J = 5.9, 8.6), 3.67 (m, 1H), 3.60 (ABq, 2H, J = 13.3, $\Delta\nu$ = 43.6), 3.34 (dd, 1H, J = 1.7, 9.7), 2.94 (dd, 1H, J = 2.1, 8.8), 2.63 (d, 1H, J = 9.1), 2.47 (app t, 1H, J = 9.3), 1.51 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$ one accidental degeneracy present in aryl region) δ 175.4 (s), 139.0 (s), 137.6 (s), 128.7 (d), 128.3 (d), 127.6 (d), 127.2 (d), 125.8 (d), 97.5 (s), 73.3 (t), 64.9 (t), 59.8 (s), 58.4 (t), 57.8 (d), 57.0 (d), 53.6 (t), 27.2 (q); IR (film) ν 3086, 3061, 3028, 2976, 2802, 1721, 1678, 1642, 1604 cm^{-1}. Anal. Calcd for $C_{22}H_{23}BrN_2O_2$: C, 61.83; H, 5.43; N, 6.56. Found: C, 61.95; H, 5.45; N, 6.51.

Cycloadduct (*R*)-4i. To a rt solution of **1i** (40.7 mg, 0.138 mmol) and (*R*)-**3** (132 mg, 0.525 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (10 mL, 0.014 mmol). The resulting solution was heated to 37 °C and was stirred for 2 h. The reaction mixture was quenched with excess saturated, aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the organic extracts were dried (Na_2SO_4) and concentrated. The crude residue was purified by radial chromatography (5:95 Et_2O/CH_2Cl_2) to give 60.6 mg (99.5%) of (*R*)-**4i** as a pale yellow oil. An analytical sample was prepared by inducing crystallization (Et_2O/hexanes), followed by trituration, to afford a pale yellow crystalline powder: R_f 0.61 (1:1 EtOAc/hexanes); mp 100−108 °C; $[\alpha]^{25}_D$ +103 (*c* 3.40, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.27 (app t, 1H, J = 6.4), 4.61 (app t, 1H, J = 7.9), 4.29 (dd, 1H, J = 5.7, 8.5), 3.49 (m, 2H), 3.28 (q, 1H, J = 6.6), 2.94 (dd, 1H, J = 2.2, 8.7), 2.50 (t, 1H, J = 9.1), 2.49 (d, 1H, J = 9.3), 1.54 (s, 3H), 1.32 (d, 3H, J = 6.5); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.6 (s), 144.2 (s), 139.3 (s), 129.1 (d), 128.8 (d), 128.0 (d), 127.5 (d), 127.1 (d), 126.1 (d), 97.9 (s), 73.8 (t), 63.91 (d), 63.88 (t), 60.1 (s), 58.2 (d), 57.3 (d), 52.4 (t), 27.6 (q), 22.7 (q); IR (film) ν 3062, 3029, 2975, 1724, 1603 cm^{-1}. Anal. Calcd for $C_{23}H_{25}BrN_2O_2$: C, 62.59; H, 5.71; N, 6.35. Found: C, 62.69; H, 5.95; N, 6.19.

Cycloadduct (*S*)-4i. To a rt solution of **1i** (32.2 mg, 0.109 mmol) and (*S*)-**3** (54.8 mg, 0.218 mmol) in CH_2Cl_2 (0.5 mL) was added a 0.13 M solution of TFA in CH_2Cl_2 (0.10 mL, 0.013 mmol). The resulting solution was stirred for 46 h at 25 °C. The reaction mixture was quenched with excess saturated, aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the organic extracts were dried (Na_2SO_4) and concentrated. Integration of the resolved signals corresponding to the major isomer ((*S*)-**4i**: δ 4.21 (dd, 1H, J = 5.7, 8.5)) and the minor isomer ((*S*)-**5i**: δ 4.08 (dd, 1H, J = 6.6, 8.4)) indicated a ratio of 91.5:8.5. The crude residue was purified by radial chromatography (5:95 Et_2O/CH_2Cl_2) to give 37.9 mg (78.8%) of (*S*)-**4i** as an off-white solid. For (*S*)-**4i:** R_f 0.44 (5:95 Et_2O/CH_2Cl_2); mp 100−103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.5 (m, 10H), 5.28 (app t, 1H, J = 6.0), 4.49 (app t, 1H, J = 8.4), 4.21 (dd, 1H, J = 5.7, 8.5), 3.86 (d, 1H, J = 8.9), 3.26 (q, 1H, J = 6.6), 3.13 (d, 1H, J = 10.0), 2.87 (dd, 1H, J = 1.8, 8.8), 2.62 (d, 1H, J = 8.9), 2.33 (app t, 1H, J = 9.4), 1.47 (s, 3H), 1.33 (d, 3H, J = 6.6); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.7 (s), 144.1 (s), 139.0 (s), 128.7 (d), 128.3 (d), 127.6 (d), 127.2 (d), 126.9 (d), 125.8 (d), 97.6 (s), 73.2 (t), 63.7 (d), 63.3 (t), 59.8 (s), 57.8 (d), 56.7 (d), 53.0 (t), 27.3 (q), 22.8 (q); IR (film) ν 3061, 3029, 2975, 1723, 1604 cm^{-1}. Anal. Calcd for $C_{23}H_{25}BrN_2O_2$: C, 62.59; H, 5.71; N, 6.35. Found: C, 62.49; H, 5.59; N, 6.36.

Cycloadducts (A)-4m and (A)-5m. Using the above general procedure, a 0 °C solution of lactam **1m** (56.0 mg, 0.186 mmol) and **2** (73.0 mg, 0.307 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.14 mL, 0.018 mmol) and was immediately allowed to warm to rt with stirring for 11 h. Integration of the resolved signals corresponding to the major isomer ((A)-**4m**: δ 0.68, 2.61, 4.33) and the minor isomer ((A)-**5m**: δ 0.62, 2.67, 4.19) indicated an average ratio of 74.3:25.7. Column chromatography (1:1 Et_2O/hexanes) of the crude mixture afforded 73.5 mg (91%) of an inseparable mixture of (A)-**4m** and (A)-**5m** as a clear, colorless, foamy film.

For (A)-**4m**, selected ^{1}H NMR signals: δ 4.33 (app t, 1H, J = 7.8), 2.61 (d, 1H, J = 9.2), 0.68 (d, 3H, J = 6.2). For (A)-**5m**, selected ^{1}H NMR signals: δ 4.19 (app t, 1H, J = 8.1), 2.67 (d, 1H, J = 9.6), 0.62 (d, 3H, J = 6.1). Anal. for a 74.3:

25.7 mixture of (A)-**4m** and (A)-**5m**; calcd for $C_{26}H_{30}N_2O_4$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.80; H, 6.94; N, 6.38.

Cycloadducts (*R*)-4m and (*R*)-5m. Using the above general procedure, a 0 °C solution of lactam **1m** (33.1 mg, 0.110 mmol) and (*R*)-**3** (33.9 mg, 0.135 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.14 mL, 0.018 mmol) and was immediately allowed to warm to rt with stirring for 10 h. Integration of the resolved signals corresponding to the major isomer ((*R*)-**4m**: δ 0.69, 2.43, 4.36) and the minor isomer ((*R*)-**5m**: δ 0.62, 2.72, 4.16) indicated an average ratio of 87.3:12.7. Radial chromatography (1:4 EtOAc/hexanes) of the crude mixture afforded 38.8 mg (79%) of pure (*R*)-**4m** as a white crystalline solid.

For (*R*)-**4m:** R_f 0.22 (1:1 (Et_2O/hexanes); mp 183−185 °C; $[\alpha]_D = +17.6$ (*c* 1.16, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$ the signals indicated by * show non-first-order behavior (virtual coupling)) δ 7.45−7.50 (m, 2H), 7.15−7.40 (m, 8H), 4.36 (dd, 1H, *J* = 7.4, 8.2), 3.7−3.8 (m, 2H), 3.68 (s, 3H), 3.59 (dd, 1H, *J* = 6.6, 8.3), 3.31 (d, 1H, *J* = 9.3), 3.22 (q, 1H, *J* = 6.5), 3.01 (dd, 1H, *J* = 1.8, 8.1), 2.43 (d, 1H, *J* = 9.3), 2.28 (app t, 1H, *J* = 8.8), 1.33 (d, 3H, *J* = 6.6), 1.13 (m, 1H), 1.04 (d, 3H, *J* = 6.2)*, 0.70 (d, 3H, *J* = 6.4)*. ^{13}C NMR (75.5 MHz, $CDCl_3$ one accidental degeneracy is present) δ 176.7 (s), 170.3 (s), 144.7 (s), 144.0 (s), 128.4 (d), 128.0 (d), 127.0 (d), 126.8 (d), 125.1 (d), 99.7 (s), 71.7 (t), 66.0 (s), 63.7 (d), 62.7 (d), 59.4 (t), 53.1 (d), 52.8 (q), 52.7 (t), 32.2 (d), 22.8 (q), 20.6 (q), 18.7 (q); IR (film) ν 2969, 1723, 1452, 1342, 1235, 962, 808 cm^{-1}. Anal. Calcd for $C_{27}H_{32}N_2O_4$: C, 72.30; H, 7.19; N, 6.25. Found: C, 72.05; H, 7.25; N, 6.17.

Cycloadducts (*S*)-4m and (*S*)-5m. Using the above general procedure, a 0 °C solution of lactam **1m** (20.0 mg, 0.0664 mmol), and (*S*)-**3** (25.0 mg, 0.0994 mmol) in CH_2Cl_2 was treated with a 0.13 M solution of TFA in CH_2Cl_2 (0.14 mL, 0.018 mmol) and was immediately allowed to warm to rt with stirring for 3 h. Integration of the resolved signals corresponding to the major isomer ((*S*)-**4m**: δ 2.07, 2.57, 3.52) and the minor isomer ((*S*)-**5m**: δ 1.97, 2.46, 3.32) indicated an average ratio of 69.1:30.9. Preparatory thin-layer chromatography (4:5 Et_2O/hexanes) of the crude mixture afforded 27.4 mg (92%) of separable mixture of (*S*)-**4m** (white crystalline solid) and (*S*)-**5m** (oil).

For (*S*)-**4m**: mp 166.5−167 °C; R_f 0.53 (4:5 Et_2O/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$ the signals indicated by * show non-first-order behavior (virtual coupling)) δ 7.41 (m, 2H), 7.27 (m, 8H), 4.33 (dd, 1H, *J* = 7.6, 8.3), 3.74 (m, 2H), 3.74 (s, 3H), 3.51 (dd, 1H, *J* = 7.0, 8.4), 3.39 (d, 1H, *J* = 9.5), 3.17 (q, 1H, *J* = 6.6), 2.91 (dd, 1H, *J* = 1.2, 8.0), 2.56 (d, 1H, *J* = 8.9), 2.07 (dd, 1H, *J* = 8.2, 9.5), 1.31 (d, 3H, *J* = 6.6), 1.07 (m, 4H), 0.68 (d, 3H, *J* = 6.2)*; ^{13}C NMR (75.5 MHz, $CDCl_3$ one accidental degeneracy is present) δ 177.1 (s), 170.3 (s), 145.2 (s), 143.7 (s), 128.4 (d), 128.2 (d), 128.0 (d), 126.9 (d), 125.1 (d), 99.8 (s), 71.6 (t), 66.1 (s), 64.1 (d), 62.7 (d), 58.8 (t), 53.9 (t), 52.9 (q), 52.8 (d), 32.4 (d), 23.6 (q), 20.7 (q), 18.6 (q); IR (film) ν 2972, 1747, 1721, 1453 cm^{-1}.

For (*S*)-**5m**: R_f 0.45 (4:5 Et_2O/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$ the signal indicated by * shows non-first-order behavior (virtual coupling)) δ 7.44 (m, 10H), 4.21 (dd, 1H, *J* = 7.7, 8.1), 3.71 (s, 3H), 3.66 (m, 1H), 3.31 (dd, 1H, *J* = 7.4, 8.4), 3.22 (d, 1H, *J* = 6.7), 3.21 (d, 1H, *J* = 9.9), 3.01 (q, 1H, *J* = 6.6), 2.44 (d, 1H, *J* = 9.9), 2.32 (d, 1H, *J* = 9.9), 1.96 (dd, 1H, *J* = 7.0, 10.0), 1.10 (m, 4H), 0.92 (d, 3H, *J* = 6.6), 0.63 (d, 3H, *J* = 6.4)*; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.8 (s), 170.5 (s), 144.6 (s), 138.0 (s), 128.8 (d), 128.6 (d), 128.5 (d), 127.1 (d), 126.7 (d), 125.8 (d), 103.9 (s), 77.2 (s), 70.1 (t), 65.6 (d), 64.0 (d), 59.3 (t), 54.2 (t), 53.0 (q), 51.1 (d), 32.2 (d), 22.4 (q), 21.0 (q), 18.6 (q); IR (film) ν 2970, 1747, 1722 cm^{-1}.

Preparation of Imide 10. To a rt mixture of maleic anhydride (200 mg, 2.04 mmoles) and dipole precursor **2** (726 mg, 3.06 mmol) was added THF (2 mL). After a few seconds, an exotherm was observed; apparently, the presence of trace acid was sufficient to catalyze the dipolar cycloaddition reaction. After 15 min, a solution of (*S*)-phenylglycinol (280 mg, 2.04 mmol) in THF (2 mL) was added dropwise to the originally clear, colorless reaction mixture to give a pale yellow gelatinous precipitate that was allowed to stir for 1 h. This precipitate was diluted with Ac_2O (20 mL) and NaOAc (0.3 g), and the mixure was heated to reflux for 2 h. The excess Ac_2O was removed by short-path distillation at atmospheric pressure, and the residue was diluted with 2 N ethanolic HCl (25 mL) and was heated to reflux for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (150 mL) and was extracted with EtOAc. The organic extracts were combined, dried ($MgSO_4$), and concentrated to a dark brown residue that was purified by column chromatography (1:4 to 100:0 EtOAc/hexanes) to afford semipure material. Repurification of this material by radial chromatography (1:4 to 100:0 EtOAc/hexanes) afforded 138 mg (19%) of **10** as a light brown film: R_f 0.50 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 5.12 (dd, 1H, *J* = 4.5, 9.0), 4.52 (app t, 1H, *J* = 10.7), 4.06 (dd, 1H, *J* = 4.8, 12.1), 3.54 (ABq, 2H, *J* = 13.1, $\Delta\nu$ = 17.8), 3.28 (d, 2H, *J* = 9.8), 3.16 (m, 3H), 2.35 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.3 (s), 179.8 (s), 137.7 (s), 135.9 (s), 128.5 (d), 128.3 (d), 128.2 (d), 127.9 (d), 127.4 (d), 127.2 (d), 61.6 (t), 58.3 (t), 58.1 (d), 56.7 (t), 56.6 (t), 44.2 (d), 44.1 (d); IR (film) ν 3454, 3087, 3063, 3031, 2964, 1954, 1770, 1694, 1651, 1633 cm^{-1}.

Reductive Dehalogenation of (*S*)-5g with Zinc. Freshly prepared zinc−copper couple (78 mg, ∼1.2 mmol) was added to a rt suspension of (*S*)-**5g** (102 mg, 0.239 mmol) and NH_4Cl (13 mg, 0.243 mmol) in MeOH (5 mL). After 20 min of stirring, TLC analysis indicated complete consumption of (*S*)-**5g**. The reaction mixture was quenched with saturated, aqueous $NaHCO_3$ to give an emulsion which was repeatedly extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford, after radial chromatography (1:1 EtOAc/hexanes), 59.7 mg (71.7%) of (*S*)-**5c** and 9.4 mg of **15** as an oil.

For **15**: R_f 0.14 (1:1 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 6.11 (d, 1H, *J* = 2.8), 5.38 (d, 1H, *J* = 2.4), 5.15 (app t, 1H, *J* = 7.4), 5.09 (s, 1H), 4.56 (app t, 1H, *J* = 8.5), 3.84 (dd, 1H, *J* = 7.1, 8.7), 3.79 (q, 1H, *J* = 6.6), 2.98 (m, 1H), 2.86 (dd, 1H, *J* = 5.0, 11.9), 2.64 (dd, 1H, *J* = 8.8, 11.9), 1.55 (br s, D_2O exch.), 1.36 (d, 3H, *J* = 6.6).

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