Stereoselective Bromination of Dehydroamino Acids with Controllable Retention or Inversion of Olefin Configuration

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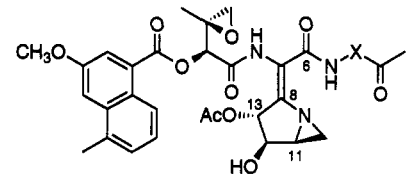
Dehydroamino acid esters react with brominating reagents to produce *syn*-α-bromo imines as the major products, which undergo tautomerization to mixtures of the diastereomeric (*E*)- and (*Z*)-β-bromo-α,β-dehydroamino acids upon treatment with base. Herein, we examine the characteristics of dehydroamino acid substrates **1** that affect both the diastereofacial selectivity of the bromination and the configuration of the resulting olefin product(s) **3**. In these studies, we demonstrate *E*- and *Z*-diastereoselectivity for this reaction using kinetic and thermodynamic reaction conditions. *Z*-Vinyl bromides were shown to be the thermodynamically more stable products and were formed from the kinetic *E*-isomers by DABCO-induced isomerization. High levels of kinetic *E*-selectivity were obtained by treatment of the intermediate α-bromo imines with hindered amine bases such as 2,2,6,6-tetramethylpiperidine or sodium hexamethyldisilazide. The reaction conditions detailed herein allow for the *stereodivergent* preparation of both *E*- and *Z*-vinyl bromide products from *either* diastereomeric *E*- or *Z*-olefin starting material with useful levels of diastereoselectivity.

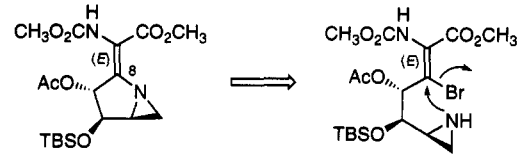
Introduction

We recently reported[2] an enantioselective synthesis of the C6–C13 aziridino[1,2-*a*]pyrrolidine substructure characteristic of the antitumor agents azinomycins A and B.[3,4] This synthesis provided for the diastereoselective introduction of the C7–C8 *E*-double bond and C12–C13 protected diol of these structurally unique natural products. During the course of this synthetic effort,[2] we encountered an intriguing, highly diastereoselective bromination of an intermediate dehydroamino acid (α-aminoacrylate). The stereocontrolled introduction of the C7–C8 tetrasubstituted olefin of the azinomycins relied critically on the sense of diastereoselection in this bromination.

Pyrrolidine ring introduction was accomplished by an intramolecular Michael addition–elimination reaction sequence between an aziridine nitrogen and an (*E*)-β-bromoacrylate in the formation of the N–C8 bond. This reaction was found to occur with complete stereospecificity, such that the *E*-stereochemical configuration of the β-bromoacrylate was transferred to the *E*-olefin of the resulting target substructure. As a result of this stereospecific pyrrolidine cyclization, we required a stereoselective synthesis of the corresponding (*E*)-α-amino-β-bromoacrylate systems. Herein, we report our observations on the bromination of dehydroamino acids[5] that have led to a better understanding of the stereoselectivity of this reaction, and we describe synthetic protocols for the divergent formation of either the (*E*)- and (*Z*)-α-amino-β-bromoacrylate systems with near complete stereochemical control of olefin configuration.



Azinomycin A (X = CH_2)
Azinomycin B (X = CH=CHOH)



Dehydroamino acid esters **1** react with brominating reagents to produce α-bromo imines **2**, which undergo tautomerization to mixtures of the diastereomeric (*E*)- and (*Z*)-β-bromo-α,β-dehydroamino acids **3** upon treatment with base.[2,5] Results reported for the diastereoselectivity of the bromination under similar reaction con-

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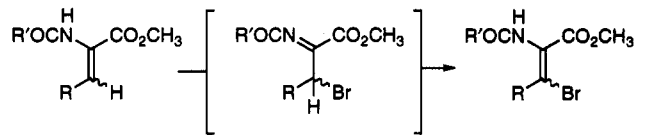
ditions are inconsistent,[5] and do not permit a clear understanding of the stereoselectivity of this process. Herein, we examine the characteristics of dehydroamino acid substrates 1 that affect both the diastereofacial selectivity of the bromination and the configuration of the resulting olefin product(s) 3, and we extend a rationale that accounts for the dissimilar observations of diastereoselectivity that have appeared in the literature.[2,4a,b,5] In these studies, we demonstrate *E*- and *Z*-diastereoselectivity for this reaction using kinetic and thermodynamic reaction conditions, which effect introduction of the tetrasubstituted olefin of 3 with useful levels of stereoselection, in a controllable manner.



1 2 3

Literature reports of dehydroamino acid brominations have suggested various intermediates in this reaction, including dibromides,[5b] *N*-bromo compounds,[4a,5a] and α-bromo iminium species,[4a] although without evidence of structure; some proposals[4a] have been revised upon more careful examination.[5b] Our investigation of this bromination clearly showed that the isolable α-bromo imine intermediate 2 was produced by reaction of dehydroamino acids 1 with *N*-bromosuccinimide (NBS),[2] a result that was in accord with previously documented reports.[5c] Moreover, our studies demonstrated that bromination–tautomerization reactions of substrates related to (*Z*)-1 (R = alkyl, R′ = OCH_3) with NBS (1.0 equiv, CH_2Cl_2, 24 °C; 1.0 equiv DABCO, 15 min) produced good yields of the corresponding *Z*-vinyl bromide ((*Z*)-3), in a highly stereoselective process that occurred with *complete inversion* of olefin configuration (≤1:20 *E*/*Z*); unfortunately, this *Z*-stereoselectivity was unsuitable for our purposes.[2] Similar *Z*-stereoselectivity was observed by Armstrong and Moran in their synthesis of the incorrect isomer of an azinomycin substructure.[4b] Our present efforts were undertaken, in part, to reconcile the disparate observations of *Z*-selectivity[2,4b,5a,e,h] versus *E*-selectivity[4a,5c,d,h] reported for the bromination of dehydroamino acids.

Examination of literature precedent on dehydroamino acid halogenations revealed no correlation of either reaction conditions or substrate functionality with reaction diastereoselectivity. Similarly, no mechanistic interpretation of this reaction pathway was evident.[4a,b,5] For example, Stammer and co-workers report an E-selective bromination of *N*-benzoyldehydroalanine using Br_2 and DABCO,[5d] whereas Kolar and Olsen report that the chlorination of *N*-acetyldehydroalanine with Cl_2 affords the corresponding *E*- and *Z*-vinyl chlorides in a 90:10 *E*/*Z* ratio using DBU or KO*t*-Bu, but in a 20:80 *E*/*Z* ratio with DABCO as the base.[5h] Danion and co-workers report obtaining the *E*- and *Z*-isomers in a 65:35 *E*/*Z* ratio in the chlorination of ethyl *N*-carbomethoxy-2-aminocinnamate with *tert*-butyl hypochlorite and Et_3N,[5c] whereas Matsumoto and co-workers demonstrated that bromination of methyl *N*-formyl-2-aminoacrylate derivatives was consistently and highly *Z*-selective when NBS was used as the halogenating agent.[5e] Das and co-workers recently reported a 1:9 *E*/*Z* ratio in the bromination of a more elaborate dehydroamino acid using Br_2 and Et_3N at −78 to 0 °C.[5a]

Armstrong and co-workers have reported that bromination of azinomycin-related dehydroamino acids with Br_2 and DABCO is completely *Z*-selective,[4b] moderately *Z*-selective (1:2.5 *E*/*Z*),[4a] or poorly *E*-selective (1.5:1 *E*/*Z*)[4a] using analogous substrates under similar reaction conditions, and that bromination of these *E*- or *Z*-dehydroamino acids with NBS in the absence of added base affords an intermediate that is converted exclusively to the corresponding *E*-vinyl bromide simply upon standing.[4a,6] In further studies,[5b] this group reported that bromination of similar dehydroamino acids with Br_2 and DABCO was highly stereoselective for the *Z*-vinyl bromide (1:15 *E*/*Z*), whereas Br_2 and Et_3N afforded predominately the *Z*-isomer, but with lower selectivity (1:3.8 *E*/*Z*). Likewise, reaction of dehydroamino acids with NBS or NIS followed by treatment with Et_3N was reported to be *Z*-selective (1:2.5 *E*/*Z*).[5b]

From the above discussion, it is apparent that the mechanistic and stereochemical behavior of this apparently well-studied reaction is by no means unambiguous, and it was from this inconsistent body of literature that we undertook our studies ultimately aimed at providing a stereoselective synthesis of the (*E*)-β-bromo-α,β-dehydroamino acids required for our azinomycin synthetic efforts.[2] Herein, we present our results on the diastereoselective bromination of dehydroamino acids and report a mechanistic rationale that ties together the dissimilar findings that have been reported on the stereochemical course of this reaction.[2,4a,b,5] Most importantly, we define reaction conditions that allow for the stereodivergent preparation of both *E*- and *Z*-vinyl bromide products from either diastereomeric *E*- or *Z*-olefin starting material in excellent chemical yield and with near complete diastereoselectivity.

Results

Dehydroamino acid substrates were prepared by Wadsworth–Horner–Emmons olefination[7] of the appropriate aldehydes 4 with the corresponding glycine phosphonates 5[7a] (Table I), using reaction conditions identical to those detailed by Schmidt and co-workers,[7a] to afford olefins 6. The yields for this process typically ranged from 73–95%. In accord with literature predecent,[7a] potassium bases provided a predominance of the *Z*-olefins, whereas lithium bases provided an increased proportion of the *E*-olefin. In all cases, the individual isomers of olefins 6 were separable by careful flash chromatography using silica gel.

Our results obtained in the bromination of dehydroamino acids **6a–f**, structurally related to those previously described,[2] are presented in Table II. Reactions were performed by treatment of the *E*- or *Z*-olefin substrates 6 with *N*-bromosuccinimide (1.0 equiv) in $CDCl_3$ at 24 °C to afford a mixture of the intermediate *syn*- and *anti*-α-bromo imines 7 in the indicated ratios. Subsequent addition of amine base (DABCO, 1.0 equiv, 24 °C, 15 min) to the reaction mixture effected rapid tautomerization of

(6) In this example,[4a] the dehydroamino acid substrate contained an *N*-tritylaziridine, which was subsequently postulated[5b] to participate as a base in the tautomerization of an α-bromo imine to the corresponding *E*-vinyl bromide. No mechanistic rationale was presented to explain the observed *E*-selectivity.

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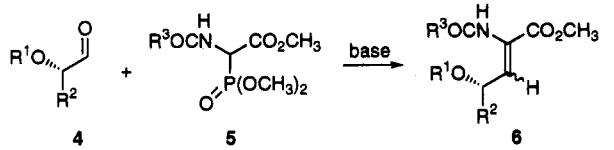
Table I. Preparation of Dehydroamino Acids[a]



4 5 6

aldehyde			phosphonate		conditions,[b]	Z/E	olefin
R[1]	R[2]	no.	R[3]	no.	% yield	ratio	no.
t-BuMe$_2$Si	CH_3	4a	OCH_3	5a	B, 75	2.2:1	6a
$PhCH_2$	CH_3	4b	OCH_3	5a	A, 77	Z only	6b
$PhCH_2$	CH_3	4b	OCH_3	5a	B, 88	1.5:1	6b
$PhCH_2$	CH_3	4b	OCH_3	5a	C, 73	3:1	6b
$PhCH_2$	CH_3	4b	Ph	5b	B, 90	5.5:1	6c
$PhCH_2$	$CH(CH_3)_2$	4c	OCH_3	5a	B, 86	1.2:1	6d
$PhCH_2$	$CH(CH_3)_2$	4c	Ph	5b	B, 95	3.0:1	6e

[a] Reference 7a. [b] A = KO*t*-Bu, CH_2Cl_2; B = LDA, THF; C = NaH, THF.

the diastereomeric α-bromo imines 7 to the *E*- and *Z*-vinyl bromides 8. Isomer ratios were determined by integration of product resonances in the crude ^{1}H NMR, and the values presented in Tables II–IV have been averaged. For comparative purposes, it is important to note that the ordering of substituents about the double bond in *E*-vinyl bromides 8 is identical to that in *Z*-dehydroamino acids 6 (*i.e.*, (*Z*)-6 corresponds to (*E*)-8).

All substrates examined showed a propensity to undergo *syn*-selective bromination and *Z*-selective tautomerization using the above reaction conditions,[2,4a,b,5d,h] without relation to the starting olefin configuration or protecting group variation. As the size of the alkyl group of the starting material was increased (R^2 = Me → *i*-Pr), both the facial selectivity of the bromination and the *Z*-selectivity of the tautomerization improved. Similarly, an amide N-protecting group induced a significantly higher *Z*-selectivity in the bromination than a carbamate, when R^2 = *i*-Pr. In no instance was the desired *E*-vinyl bromide produced in this reaction as the predominant isomer.

From examination of these results (Table II), there appeared to be a moderate correlation between the bromination *syn*-selectivity and the tautomerization *Z*-selectivity. These results suggested several possible mechanistic interpretations: (1) the tautomerization of α-bromo imines *syn*-7 and *anti*-7 were only moderately stereoselective, with the *syn*-isomer leading predominately to the *Z*-vinyl bromide, and the *anti*-isomer to the *E*-isomer; (2) base-promoted epimerization of the intermediate α-bromo imines was occurring prior to a highly stereoselective (syn → *Z*, anti → *E*) tautomerization, thereby altering the correlation between anti/syn and *E*/*Z* ratios; (3) the *E*- and *Z*-vinyl bromide products were equilibrating under the reaction conditions, and that there was no relationship between *syn*-selectivity and *Z*-selectivity. Clearly, these experiments did not allow us to establish a convincing mechanistic rationale that accounted for the stereochemical course of this reaction, nor did the results provide evidence for a significant effect of substrate functionality on reaction diastereoselectivity. Despite the failure of these experiments to provide a conclusive stereochemical pathway for the reaction, the results raised several important questions: (1) why was the *Z*-vinyl bromide consistently obtained as the predominant isomer, when computer and molecular models predicted that the transition state for proton transfer leading from the intermediate α-bromo imine 7 to the *E*-isomer should be energetically favored; (2) what was the individual diastereoselectivity for the tautomerization of isomerically pure *syn*- and *anti*-α-bromoimines 7; (3) was there a base-promoted mechanism operating to interconvert or equilibrate the *Z*- and *E*-vinyl bromides 8?

Examination of the tautomerization diastereoselectivity of the isomerically pure *syn*- and *anti*-α-bromo imines **7b** provided considerable insight into the mechanism of this reaction. The major α-bromo imine (*syn*-**7b**) could be isolated from the bromination reaction of (*Z*)-**6b** (1.0 equiv NBS, $CDCl_3$, 24 °C) as a single diastereomer by careful, rapid chromatography on silica gel, whereas the minor diastereomer (*anti*-**7b**) was significantly more difficult to purify to acceptable homogeneity. The separated, diastereomerically pure isomers were subjected to base-promoted tautomerization in $CDCl_3$, and the reactions were monitored and analyzed *in situ* by ^{1}H NMR (500 MHz). The results are presented in Table III.

Treatment of *syn*-**7b** with DABCO (1.0 equiv, 24 °C, 15 min) afforded the corresponding vinyl bromides **8b** nonselectively in a 1:1.2 *E*/*Z* ratio (Table III). However, after 4.5 h at 24 °C, the proportion of *Z*-vinyl bromide had increased significantly, and complete isomerization occurred over the course of 72 h to afford the *Z*-vinyl bromide as a single diastereoisomer (≤1:20 *E*/*Z*). This outcome provided the first evidence that the ratio of *E*- to *Z*-vinyl bromide reaction products was experimentally manipulable. Evaluation of this result led us to the conclusion that the *Z*-vinyl bromide was the thermodynamically more stable product and was being formed from the presumed kinetic *E*-isomer by a DABCO[8] or base-induced isomerization.[9] Thus, it seemed reasonable to examine more sterically hindered bases and lower reaction temperatures in anticipation of obtaining an increased proportion of the kinetic *E*-isomer of **8b**.[10]

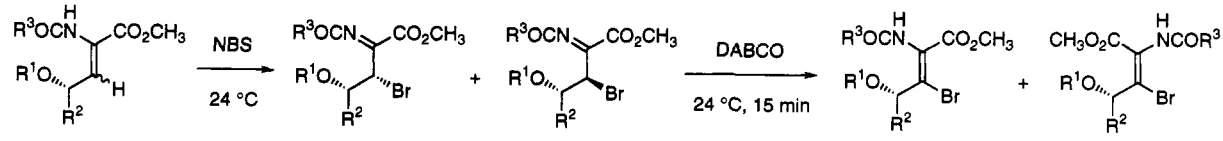
In confirmation of this hypothesis, treatment of *syn*-**7b** with Et_3N (1.0 equiv, 24 °C) afforded the vinyl bromides **8b** in a modest but gratifying 2.6:1 *E*/*Z* ratio (Table III), which was unchanged upon extended exposure to these conditions (36 h, 24 °C). When this same reaction mixture subsequently was treated with DABCO (1.0 equiv), *complete isomerization* of the kinetic *E*-isomer to the apparently more stable *Z*-isomer of **8b** was effected over 72 h, a result that was consistent with a DABCO-induced *E* to *Z* isomerization. Similarly, treatment of *syn*-**7b** with DBU (1.0 equiv, 24 °C) afforded the *E*-vinyl bromide **8b** in a 2.3:1 ratio to the *Z*-isomer, and this ratio also was unchanged upon extended reaction times. The most effective amine base for kinetically controlled formation of the *E*-vinyl bromide from *syn*-**7b** was 2,2,6,6-tetramethylpiperidine (TMP), which afforded the isomeric vinyl bromides in a promising 8:1 *E*/*Z* ratio at 24 °C, and in an exceptional 17:1 ratio at −20 °C. Sodium hexamethyl-

(8) (a) Basavaiah, D.; Gowriswari, V. V. L.; Sarma, P. K. S.; Dharma Rao, P. *Tetrahedron Lett.* **1990**, *31*, 1621. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 6095.

(9) Base-promoted isomerization of dehydrophenylalanine derivatives has been reported: Nitz, T. J.; Holt, E. M.; Rubin, B.; Stammer, C. H. *J. Org. Chem.* **1981**, *46*, 2667. This report postulated that the isomerization was due to N-deprotonation followed by isomerization of a delocalized anion. In the present studies, base-promoted isomerization was not observed upon extended exposure of the kinetic *E*-vinyl bromide to strongly basic reaction conditions (Et_3N, DBU, or TMP).

(10) The possibility of kinetic control in the bromination of dehydroamino acids has been raised by Combs and Armstrong[6b] prior to our studies. However, in their study no selectivity for the purported kinetic *E*-vinyl bromide was obtained, although isomerization of a purified *E*-vinyl bromide to the corresponding *Z*-isomer was reported to occur in the presence of DABCO.

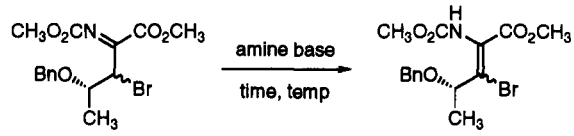
Table II. Bromination with *N*-Bromosuccinimide/DABCO



(*Z*)-6 (*E*)-6 *syn*-7 *anti*-7 (*E*)-8 (*Z*)-8

	olefin					
compound no.	R^1	R^2	R^3	syn/anti ratio of 7	*E*/*Z* ratio of 8	vinyl bromide
(*Z*)-**6f**	CH_3CO	CH_3	OCH_3	2.6:1	1:3.2	**8f**
(*Z*)-**6a**	*t*-$BuMe_2Si$	CH_3	OCH_3	5.3:1	1:1.7	**8a**
(*E*)-**6a**	*t*-$BuMe_2Si$	CH_3	OCH_3	4.3:1	1:1.8	**8a**
(*Z*)-**6b**	$PhCH_2$	CH_3	OCH_3	3.1:1	1:1.8	**8b**
(*E*)-**6b**	$PhCH_2$	CH_3	OCH_3	3.7:1	1:1.8	**8b**
(*Z*)-**6c**	$PhCH_2$	CH_3	Ph	7.1:1	1:1.3	**8c**
(*E*)-**6c**	$PhCH_2$	CH_3	Ph	13:1	1:1.5	**8c**
(*Z*)-**6d**	$PhCH_2$	$CH(CH_3)_2$	OCH_3	8:1	1:5.3	**8d**
(*E*)-**6d**	$PhCH_2$	$CH(CH_3)_2$	OCH_3	5.0:1	1:5.3	**8d**
(*Z*)-**6e**	$PhCH_2$	$CH(CH_3)_2$	Ph	≥20:1	1:10	**8e**
(*E*)-**6e**	$PhCH_2$	$CH(CH_3)_2$	Ph	4:1	1:13	**8e**

Table III. Stereoselective Tautomerization of α-Bromo Imines



7b **8b**

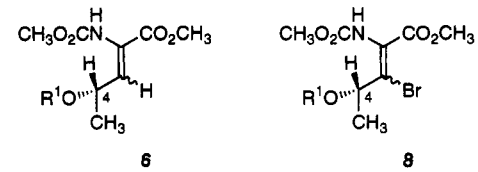
α-bromo imine	amine base, temperature, °C	time	*E*/*Z* ratio of olefin **8b**
syn-**7b**	DABCO, 24	15 min	1:1.2
		4.5 h	1:1.7
		36 h	1:10.1
		72 h	≤1:20
syn-**7b**	Et_3N, 24	15 min	2.6:1
		2 h	2.5:1
		36 h	2.5:1
	DABCO, 24	15 min	2.5:1
		16 h	1:3.4
		72 h	≤1:20
syn-**7b**	DBU, 24	15 min	2.3:1
syn-**7b**	TMP, 24	2 h	8.0:1
syn-**7b**	TMP, −20	48 h	17:1
syn-**7b**	NaHMDS, −78	5 min	12.8:1
syn-**7b**	Et_3N, −20	9 h	2.8:1
anti-**7b**	TMP, 24	72 h	1:1.2
anti-**7b**	TMP, −20	10 d	1:2.9

disilazide (NaHMDS) rapidly promoted the tautomerization at −78 °C, but with slightly decreased *E*-selectivity. In contrast to the major *syn*-isomer, *anti*-**7b** proved markedly less stereoselective, and unexpectedly gave the *Z*-vinyl bromide as the major diastereomer when tautomerization was effected with TMP. In addition, *anti*-**7b** proved significantly less reactive than *syn*-**7b** toward base and required 10 days at −20 °C to undergo complete tautomerization. Base-promoted epimerization of the C3 stereogenic center of *anti*-**7b** was not observed (by ^1H NMR) during the course of this tautomerization reaction.

In the present work, DABCO was the only amine base that detectably induced this isomerization process. To confirm that this isomerization was occurring within the vinyl bromide manifold, diastereomerically pure (*E*)-**8b** was treated with DABCO (1 equiv) in $CDCl_3$ (0.21 M), conditions that effected complete isomerization to (*Z*)-**8b** (≤1:20 *E*/*Z*) after 9 h at 24 °C.

When the results presented in Table III were applied to preparative-scale brominations of dehydroamino acids, equally facile manipulation of olefin configuration of the product vinyl bromides was possible (Table IV). The kinetic selectivity was found to be slightly eroded when crude mixtures of *syn*- and *anti*-α-bromo imines were treated with TMP at −20 °C, presumably due to the *Z*-selectivity of the tautomerization of the *anti*-bromo imine isomers.

Assignment of olefin configuration of the series of dehydroamino acids (*E*)- and (*Z*)-**6** and vinyl bromides (*E*)- and (*Z*)-**8** was based primarily on correlation of ^1H NMR spectral data. Within the series of olefins **6a–e**, the vinylic C3–H and allylic C4–H protons of the *E*-isomers resonated downfield relative to the corresponding *Z*-isomers ($\Delta\delta$ = 0.16–1.0 ppm). Likewise, the NH proton of the *E*-isomers of **6a–d** resonated downfield relative to the corresponding *Z*-isomers ($\Delta\delta$ = 0.04–0.50 ppm); this correlation did not hold for **6e**. A similar correlation was observed for the NH proton of the *Z*-isomers of vinyl bromides **8a–f**, which resonated downfield relative to the corresponding *E*-isomer ($\Delta\delta$ = 0.91–1.75 ppm). Assign-



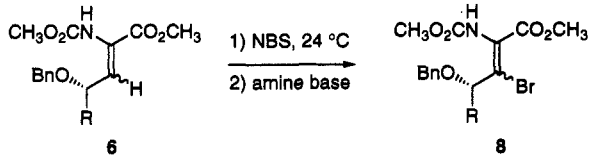
6 **8**

ment of olefin configuration of (*E*)-**8b** ($R^1 = CH_2Ph$) was confirmed as detailed previously[2] by the observation of a reciprocal, positive nuclear Overhauser enhancement of the NH and C4–H resonances in the NOE difference spectrum (500 MHz, $CDCl_3$) and by the absence of equivalent enhancements for (*Z*)-**8b**. Chemical confirmation of olefin configuration was obtained by treatment of either (*E*)-**6a** or (*Z*)-**8a** (R^1 = $SiMe_2t$-Bu) with HOAc/THF/H_2O (3:1:1) to produce the allylic alcohol. This intermediate underwent spontaneous cyclization onto the proximal *cis*-carboxylate to afford the corresponding γ-lactone, which was characterized by IR spectroscopy by observation of a carbonyl stretch at 1760 cm^{-1}.

Discussion

The results presented in Tables II and III allow us to formulate the following mechanistic rationale to account for the observed diastereoselectivity in the bromination

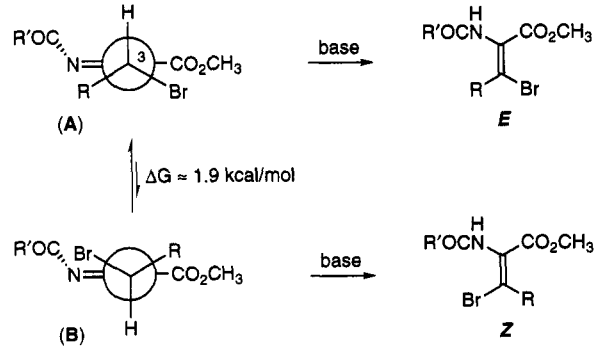
Table IV. Stereodivergent Bromination of Dehydroamino Acids



6 8

substrate	amine base, time, temp, °C	major product	isomer ratio (*E*/*Z*)	isolated yield, %
(*E*)-**6b**	TMP, 5 d, −20	(*E*)-**8b**	7.2:1	73
(*Z*)-**6b**	TMP, 5 d, −20	(*E*)-**8b**	6.7:1	79
(*E*)-**6b**	DABCO, 32 h, 24	(*Z*)-**8b**	≤1:20	69
(*Z*)-**6b**	DABCO, 32 h, 24	(*Z*)-**8b**	≤1:20	72
(*E*)-**6d**	TMP, 11 d, −20	(*E*)-**8d**	7.6:1	66
(*Z*)-**6d**	DABCO, 16 h, 24	(*Z*)-**8d**	1:6.5	73

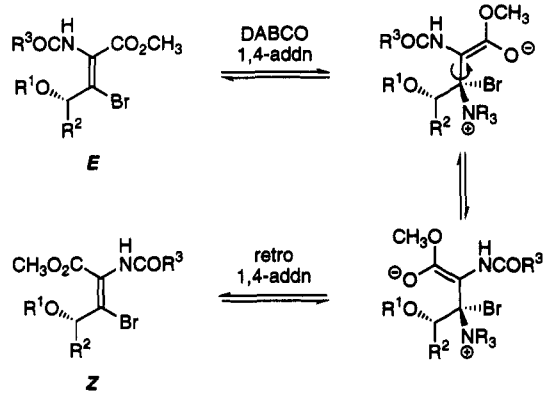
of dehydroamino acids. Stereoelectronically controlled tautomerization of an α-bromo imine to the corresponding vinyl bromide must occur by a transition state wherein the sp^3 orbital of the C3–H bond is aligned with the π-orbitals of the imine double bond (*i.e.*, ∠ H–C3–C2–N $\simeq$ 90°), in analogy to the transition state proposed for deprotonation of the carbon α to a carbonyl group.[11] The two possible ground-state conformers, **A** and **B**, that directly lead to such transition states are depicted below. Base-promoted tautomerization of rotamer **A** gives the *E*-vinyl bromide, whereas rotamer **B** gives the *Z*-vinyl bromide. Molecular mechanics calculations (MMX force-



field) provide an estimate of the energy difference between these two ground-state conformers. This calculation was performed by restricting the H–C3–C2–N dihedral angle to ±90° and gave a value of ΔG = 1.9 kcal/mol favoring conformer **A**. This energetic preference appears to be due to an unfavorable steric interaction between the bulky alkyl group R and the proximal carbomethoxy group in conformer **B**, an interaction that is absent in conformer **A**. This steric repulsion will be amplified in the corresponding transition state leading from **B** to the *Z*-vinyl bromide, as the incipient sp^2-hybridized C3 forces the interacting groups into closer proximity. The consequent energy difference likewise will be increased in the transition state. This analysis provides a credible explanation for the observed kinetic selectivity in the base-promoted tautomerization of α-bromo imine *syn*-**7** to *E*-vinyl bromides **8**.

The difference in stability of conformers **A** and **B** does not account completely for the observed reaction selectivity; the fact that *anti*-**7b** provided the *Z*-vinyl bromide as the major isomer under kinetic conditions is not consistent with the analysis presented above. Neither the amine base nor the additional C4 stereogenic center have been factored into the molecular mechanics calculations, although both variables significantly affect the diastereoselectivity of the tautomerization reaction. Two experimental observations are pertinent to this discussion: (1) *anti*-**7b** reacted with amine bases at dramatically reduced rates compared to *syn*-**7b**; (2) *syn*-**7b** undergoes highly *E*-stereoselective tautomerization, whereas *anti*-**7b** reacts with poor selectivity under identical reaction conditions. The differing diastereoselectivity and reactivity of *anti*-**7b** and *syn*-**7b** likely originate in complex steric interactions of the amine bases with the substrates in the reaction transition states. The opposite diastereoselectivity observed in the tautomerization of *anti*-**7b** does not invalidate the conformational analysis as presented, but merely points to more complex interactions involving the C4 stereogenic center and the amine base that play a significant role in determining the reaction selectivity with this diastereomer.

A mechanism for interconversion of the kinetically formed *E*-vinyl bromide to the thermodynamically more stable *Z*-isomer, which is induced by exposure of the kinetic *E*-vinyl bromide to DABCO, can be proposed by invoking a Michael addition–elimination reaction sequence.[8] This process is well-precedented in reactions such as the Baylis–Hillman coupling,[8] wherein acrylate esters can be alkylated at the α-position with aldehydes in the presence of DABCO. The Baylis–Hillman reaction presumably occurs through the intermediacy of the enolate produced by 1,4-addition of DABCO to the acrylate substrate, in a process that is analogous to that shown below. These reaction processes



depend upon the nucleophilic character of DABCO, as both the Baylis–Hillman coupling[8] and the $E \rightarrow Z$ isomerization in the present study occur to an appreciable extent only in the presence of this amine base.

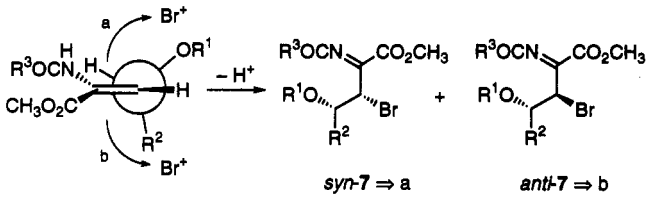
This isomerization is due to an addition–elimination reaction mechanism as opposed to the alternative base-promoted process.[9] This is evidenced by the fact that DABCO, the least hindered, most nucleophilic amine,[8] is the most effective at promoting this isomerization. Likewise, the lack of correlation between pK_{BH^+} and isomerization rate further supports this claim. Strong hindered amine bases such as tetramethylpiperidine (pK_{BH^+} = 11.07)[12a] and Et_3N (pK_{BH^+} = 10.75)[12b] are ineffective at promoting this isomerization, while the significantly weaker base DABCO (pK_{BH^+} = 8.82)[12c] is effective.

At present, we can offer no conclusive evidence for the stereochemistry of the intermediate α-bromo imines,

(11) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press: New York, 1983.

(12) (a) Hall, H. K., Jr. *J. Phys. Chem.* **1956**, *60*, 63. (b) Somerville, W. C. *J. Phys. Chem.* **1931**, *35*, 2412. (c) Paoletti, P.; Stern, J. H.; Vacca, A. *J. Phys. Chem.* **1965**, *69*, 3759.

although such an assignment is not relevant to the studies detailed herein. We have tentatively assigned the major diastereoisomer as the *syn*-α-bromo imine based on literature precedent[13] and using theoretical models of the reaction of electrophiles with allylic ethers.[14] Reaction of the nucleophilic olefin of **6** with the electrophile *N*-bromosuccinimide would be expected to occur (at least partially) via the conformation shown below, where the allylic hydrogen is nearly eclipsed with the double bond.[15] In this conformer, addition of an electrophilic bromine species would occur *syn* to the directing ether oxygen[14]



via pathway a and would lead preferentially to *syn*-**7**. This analysis is consistent with the increased stereoselectivity that was observed as the size of R^2 was increased.

Conclusion

The results obtained in our studies of the bromination of dehydroamino acids have provided firm evidence for the proposed mechanistic and stereochemical course of this reaction. We have convincingly demonstrated both kinetic and thermodynamic selectivity in the formation of *E*- and *Z*-vinyl bromides, respectively, with useful levels of stereochemical control. We have conclusively shown the existence of α-bromo imine species as stable, isolable intermediates in this reaction, and we have demonstrated their kinetically controlled tautomerization to *E*-vinyl bromides with a high degree of stereoselectivity. Furthermore, we have documented the ability of DABCO to promote the isomerization of kinetically formed *E*-vinyl bromides to the thermodynamically more stable *Z*-isomers by a conjugate addition–elimination reaction sequence. The reaction conditions detailed herein allow for the *stereodivergent* preparation of both *E*- and *Z*-vinyl bromide products from *either* diastereomeric *E*- or *Z*-olefin starting material with useful levels of diastereoselectivity. Most importantly, our studies have provided a synthetic protocol for the stereocontrolled synthesis of *E*-vinyl bromides required for our studies on the antitumor agents azinomycins A and B.[2] When our results are considered in the context of previous work in this area,[2,4a,b,5] it is apparent that several significant mechanistic and stereochemical issues have been resolved in a manner that will allow this chemistry to be applied predictively to the stereocontrolled synthesis of more highly elaborate dehydroamino acids.

Experimental Section

Methyl 2-(Dimethoxyphosphinyl)-2-[*N*-(methoxycarbonyl)amino]ethanoate (5a). Using the general procedure of Zoller and Ben-Ishai[17] for the preparation of glyoxylic acid derivatives, a stream of N_2 was passed over glyoxylic acid monohydrate (60.0 g, 0.33 mol) overnight at 24 °C. The residue was dissolved in Et_2O (300 mL), and methyl carbamate (24.5 g, 0.33 mol) was added at 24 °C. The mixture was stirred at 24 °C for 12 h, during which time a white precipitate formed. The solid was collected by filtration (Et_2O wash) to afford the crude hydroxy acid (45.0 g, 93%), which was treated with CH_3OH (400 mL) and H_2SO_4 (8 mL) at 24 °C for 2 d. The reaction mixture was concentrated to 100 mL by rotary evaporation, diluted with EtOAc (150 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × 100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to provide a pale yellow oil that was purified by flash chromatography (5.4 × 20 cm silica gel, 25–40% EtOAc/hexanes) to afford methyl 2-[*N*-(methoxycarbonyl)amino]-2-methoxyethanoate (32.8 g, 57%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (br s, 1 H, NH), 5.17 (d, J = 9.5 Hz, 1 H, C*H*NH), 3.63 (s, 3 H, CO_2CH_3), 3.56 (s, 3 H, CO_2CH_3), 3.27 (s, 3 H, CHOCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 156.8, 81.0, 56.2, 53.0, 52.8; IR (neat) ν_{max} 3332, 2954, 1733, 1225 cm^{-1}; CIMS (NH_3), m/z (rel inten) 195 (M^+ + NH_4, base), 178 (M^+ + H, 64), 163 (58), 146 (38), 118 (54); HRMS, m/z calcd for $C_6H_{11}NO_5$–OCH_3 146.0453, found 146.0446. Anal. Calcd for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.79; H, 6.30; N, 7.88.

Following the procedure of Schmidt and co-workers[7a] for the preparation of glycine phosphonates, a solution of methyl 2-[*N*-(methoxycarbonyl)amino]-2-methoxyethanoate (22.9 g, 129 mmol) in toluene (250 mL) under N_2 was treated with phosphorus trichloride (11.3 mL, 129 mmol) at 70 °C for 18 h and then with trimethyl phosphite (15.2 mL, 129 mmol) for 2 h at 70 °C. The pale yellow oil obtained by evaporative workup was filtered through a plug of silica gel (EtOAc wash) and concentrated *in vacuo* to afford a light yellow oil that crystallized upon standing. Recrystallization from EtOAc/hexanes afforded phosphonate **5a** (16.5 g, 50%) as a white powder: mp 63–65 °C (Et_2O/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (br d, J = 9.3 Hz, 1 H, NH), 4.90 (dd, $^2J_{PH}$ = 22.4 Hz, J = 9.3 Hz, 1 H, PC*H*NH), 3.83 and 3.79 (2 d, $^3J_{PH}$ = 4.6 Hz, 6 H, P(OCH_3)$_2$), 3.82 (s, 3 H, CO_2CH_3), 3.71 (s, 3 H, CO_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6 (d, $^2J_{PC}$ = 3.0 Hz, PC*C*), 156.7 (d, $^3J_{PC}$ = 8.0 Hz, PCN*C*), 54.3 and 54.2 (2 d, $^2J_{PC}$ = 6.7 Hz, P(O*C*H$_3$)$_2$), 53.4, 53.0, 52.3 (d, $^1J_{PC}$ = 49.0 Hz, P*C*); ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.5; IR (KBr) ν_{max} 3282, 1754, 1718, 1221, 1051 cm^{-1}; EIMS, m/z (rel inten) 255 (M^+, 32), 223 (79), 196 (base), 164 (93), 146 (95), 129 (82), 110 (89), 93 (94); HRMS, m/z calcd for $C_7H_{14}NO_7P$ 255.0508, found 255.0507. Anal. Calcd for $C_7H_{14}NO_7P$: C, 32.95; H, 5.53; N, 5.49. Found: C, 33.04; H, 5.54; N, 5.42.

Methyl 2-(*N*-Benzoylamino)-2-(dimethoxyphosphinyl)-ethanoate (5b). Benzoic anhydride (1.4 g, 6.0 mmol, 2.0 equiv) and 10% palladium on carbon (0.1 g, 10 wt%) were added to a solution of methyl 2-[*N*-(benzyloxycarbonyl)amino]-2-(dimethoxyphosphinyl)ethanoate[7a] (1.0 g, 3.0 mmol) in EtOAc (15 mL), which was placed under a hydrogen atmosphere (1 atm, balloon). The reaction mixture was allowed to stir for 24 h at 24 °C. The catalyst and polar materials were removed by filtration through a mixed plug of alumina and silica gel (EtOAc wash) and the filtrate was concentrated *in vacuo* to afford a pale yellow oil that crystallized upon standing. The solid was recrystallized (EtOAc/hexanes) to afford phosphonate **5b** (0.78 g, 82%) as a white crystalline solid: mp 107–109 °C (EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (m, 2 H, ArH), 7.46 (m, 1 H, ArH), 7.37 (m, 2 H, ArH), 7.31 (br d, J = 8.9 Hz, 1 H, NH), 5.43 (dd, $^2J_{PH}$ = 22.3 Hz, J = 8.9 Hz, 1 H, PC*H*NH), 3.80 and 3.74 (2 d, $^3J_{PH}$ = 11.1 Hz, 6 H, P(OCH_3)$_2$), 3.76 (s, 3 H,

(13) Reetz, M. T.; Kayser, F.; Harms, K. *Tetrahedron Lett.* **1992**, *33*, 3453.

(14) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650. Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 666.

(15) Armstrong and co-workers invoked a Felkin–Ahn transition state[16] in their analysis of dehydroamino acid brominations, although without verification of α-bromo imine stereochemistry. In separate reports from this group, both the *syn*[5b] and *anti*-α-bromo imines[4a] were assigned as the Felkin–Ahn products; clearly, the *anti*-α-bromo imine is the expected isomer based on the correct usage of a Felkin–Ahn analysis.[16] However, the theoretical work of Hehre and co-workers[14] and experimental results collated therein are inconsistent with the use of the Felkin–Ahn model to predict the stereoselectivity in reactions of chiral allylic ethers with electrophiles.

(16) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(17) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863.

CO_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5 (d, $^2J_{PC}$ = 2.3 Hz, PCC), 167.3 (d, $^3J_{PC}$ = 5.8 Hz, PhCNCP), 133.4, 132.5, 129.0, 127.8, 54.6 and 54.4 (2 d, $^2J_{PC}$ = 6.6 Hz, $P(OCH_3)_2$), 53.7, 50.8 (d, $^1J_{PC}$ = 48.6 Hz, PC); ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.6; IR (KBr) ν_{max} 3303, 3241, 1739, 1667, 1231, 1041, 759, 708 cm^{-1}; EIMS, *m/z* (rel inten) 301 (M^+, 8), 270 (10), 242 (15), 175 (29), 105 (base); HRMS, *m/z* calcd for $C_{12}H_{16}NO_6P$ 301.0715, found 301.0714. Anal. Calcd for $C_{12}H_{16}NO_6P$: C, 47.84; H, 5.35; N, 4.65. Found: C, 47.91; H, 5.35; N, 4.61.

(4*S*)-Methyl 4-(*tert*-Butyldimethylsiloxy)-2-[*N*-(methoxycarbonyl)amino]-2-pentenoate (6a). Aldehyde **4a**[18a] (0.82 g, 4.3 mmol) was subjected to Wadsworth–Horner–Emmons olefination as described by Schmidt and co-workers[7a] with phosphonate **5a** (1.4 g, 5.5 mmol, 1.3 equiv) and freshly prepared LDA (5.1 mL, 1.0 M in THF, 5.1 mmol, 1.2 equiv) in THF (20 mL) under N_2 at −78 °C for 30 min. Purification by flash chromatography (3.6 × 20 cm silica gel, 10–30% EtOAc/hexanes) afforded a separable mixture of olefins (*E*)-**6a** and (*Z*)-**6a** (1.02 g combined, 76%) as colorless oils. Pure (*E*)-**6a** was characterized: ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (br s, 2 H, overlapping NH and C=C*H*), 5.20 (dq, *J* = 8.2, 6.2 Hz, 1 H, C*H*CH_3), 3.79 (s, 3 H, CO_2CH_3), 3.67 (s, 3 H, CO_2CH_3), 1.24 (d, *J* = 6.2 Hz, 3 H, CHC*H*$_3$), 0.83 (s, 9 H, $SiC(CH_3)_3$), −0.01 and −0.02 (2 s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 155.2, 136.8, 125.2, 66.2, 53.1, 52.9, 26.1, 23.3, 18.4, −4.4, −4.8; IR (neat) ν_{max} 3343, 1739, 1251, 833, 776 cm^{-1}; FBMS, *m/z* (rel inten) 318 (M^+ + H, 10), 289 (7), 260 (43), 186 (base), 154 (72); HRMS, *m/z* calcd for $C_{14}H_{27}NO_5Si-CH_3$ 302.1424, found 302.1416. Pure (*Z*)-**6a** was characterized: ^1H NMR (300 MHz, $CDCl_3$) δ 6.62 (br s, 1 H, NH), 6.30 (d, *J* = 7.3 Hz, 1 H, C=C*H*), 4.60 (dq, *J* = 7.3, 6.4 Hz, 1 H, C*H*CH_3), 3.78 (s, 3 H, CO_2CH_3), 3.70 (s, 3 H, CO_2CH_3), 1.29 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.04 and 0.02 (2 s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 154.4, 135.6, 122.8, 66.0, 52.8, 52.6, 26.2, 24.8, 18.5, −4.2, −4.4; IR (neat) ν_{max} 3329, 1720, 1255, 831, 777 cm^{-1}; CIMS, *m/z* (rel inten) 317 (M^+, 2), 302 (18), 285 (12), 260 (90), 228 (base), 200 (32); HRMS, *m/z* calcd for $C_{14}H_{27}NO_5Si$ 317.1658, found 317.1659.

(4*S*)-Methyl 4-(Benzyloxy)-2-[*N*-(methoxycarbonyl)amino]-2-pentenoate (6b). Aldehyde **4a** (0.70 g, 4.2 mmol) was subjected to Wadsworth–Horner–Emmons olefination as described for **6a** with phosphonate **5a** (1.5 g, 5.8 mmol, 1.4 equiv) and freshly prepared LDA (5.0 mL, 1.0 M in THF, 5.0 mmol, 1.2 equiv) in THF (20 mL) under N_2 at −78 → 24 °C for 2 h. Purification by flash chromatography (1.4 × 25 cm silica gel, 10–20% EtOAc/hexanes) afforded a separable mixture of olefins (*E*)-**6b** and (*Z*)-**6b** (1.06 g combined, 88%) as colorless oils. Pure (*E*)-**6b** was characterized: ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5 H, ArH), 6.78 (m, 2 H, overlapping NH and C=C*H*), 4.92 (dq, *J* = 8.5, 6.4 Hz, 1 H, C*H*CH_3), 4.43 (AB q, *J* = 11.8 Hz, $\Delta\nu$ = 59.8 Hz, 2 H, OCH_2Ph), 3.75 (s, 3 H, CO_2CH_3), 3.72 (s, 3 H, CO_2CH_3), 1.33 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 154.1, 138.6, 131.6, 128.3, 127.8, 127.5, 125.6, 71.2, 70.6, 52.5, 52.4, 21.4; IR (neat) ν_{max} 3330, 1732, 1249, 739, 699 cm^{-1}; EIMS, *m/z* (rel inten) 293 (M^+, 10), 261 (15), 218 (14), 202 (20), 160 (45), 128 (43), 91 (base); HRMS, *m/z* calcd for $C_{15}H_{19}NO_5$ 293.1263, found 293.1264. Pure (*Z*)-**6b** was characterized: ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5 H, ArH), 6.38 (br s and d, *J* = 8.4 Hz, 2 H, overlapping NH and C=C*H*), 4.43 (AB q, *J* = 11.8 Hz, $\Delta\nu$ = 29.8 Hz, 2 H, OCH_2Ph), 4.35 (dd, *J* = 8.4, 6.3 Hz, 1 H, C*H*CH_3), 3.79 (s, 3 H, CO_2CH_3), 3.69 (s, 3 H, CO_2CH_3), 1.36 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 155.0, 138.2, 135.9, 128.4, 127.8, 127.6, 126.9, 71.1, 70.8, 52.7, 52.6, 19.8; IR (neat) ν_{max} 3305, 1732, 1661, 1237, 778, 740, 699 cm^{-1}; EIMS, *m/z* (rel inten) 293 (M^+, 4), 261 (10), 241 (12), 202 (33), 160 (61), 128 (48), 91 (base); HRMS, *m/z* calcd for $C_{15}H_{19}NO_5$ 293.1263, found 293.1250.

(4*S*)-Methyl 2-(*N*-Benzoylamino)-4-(benzyloxy)-2-pentenoate (6c). Aldehyde **4b**[18a] (0.50 g, 3.0 mmol) was subjected to Wadsworth–Horner–Emmons olefination as described for **6a** with phosphonate **5b** (1.2 g, 3.9 mmol, 1.3 equiv) and freshly prepared LDA (3.6 mL, 1.0 M in THF, 3.6 mmol, 1.2 equiv) in THF (25 mL) under N_2 at −78 → 24 °C for 4 h. Purification by flash chromatography (2.6 × 25 cm silica gel, 20–40% EtOAc/hexanes) afforded a separable mixture of olefins (*E*)-**6c** and (*Z*)-**6c** (0.90 g combined, 90%) as colorless oils. Pure (*E*)-**6c** was characterized: ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (br s, 1 H, NH), 7.81 (m, 2 H, ArH), 7.52 (m, 1 H, ArH), 7.46 (m, 2 H, ArH), 7.35–7.23 (m, 6 H, overlapping C=C*H* and ArH), 4.97 (dq, *J* = 8.6, 6.4 Hz, 1 H, C*H*CH_3), 4.53 (AB q, *J* = 11.9 Hz, $\Delta\nu$ = 103.3 Hz, 2 H, OCH_2Ph), 3.80 (s, 3 H, CO_2CH_3), 1.39 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 164.6, 138.6, 134.5, 134.0, 132.0, 128.8, 128.3, 127.8, 127.5, 127.0, 125.6, 71.4, 70,8, 52.7, 21.4; IR (neat) ν_{max} 3303, 1728, 1651, 1518, 739, 697 cm^{-1}; EIMS, *m/z* (rel inten) 339 (M^+, 3), 248 (8), 204 (49), 172 (23), 128 (20), 105 (base); HRMS, *m/z* calcd for $C_{20}H_{21}NO_4$ 339.1471, found 339.1459. Pure (*Z*)-**6c** was characterized: ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (br s, 1 H, NH), 7.66 (m, 2 H, ArH), 7.49 (m, 1 H, ArH), 7.36 (m, 2 H, ArH), 7.32–7.24 (m, 5 H, ArH), 6.35 (d, *J* = 7.3 Hz, 1 H, C=C*H*), 4.49 (AB q, *J* = 11.5 Hz, $\Delta\nu$ = 16.0 Hz, 2 H, OCH_2Ph), 4.39 (dq, *J* = 7.3, 6.4 Hz, 1 H, C*H*CH_3), 3.80 (s, 3 H, CO_2CH_3), 1.41 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 165.1, 137.9, 133.3, 132.9, 132.1, 128.7, 128.5, 128.0, 127.9, 127.6, 127.4, 72.2, 71.0, 52.7, 19.6; IR (neat) ν_{max} 3308, 1730, 1648, 1251, 913, 740, 699 cm^{-1}; EIMS, *m/z* (rel inten) 339 (M^+, 2), 248 (17), 204 (26), 172 (15), 128 (20), 105 (base); HRMS, *m/z* calcd for $C_{20}H_{21}NO_4$ 339.1471, found 339.1468.

(4*R)-Methyl 4-(Benzyloxy)-2-[*N*-(methoxycarbonyl)amino]-5-methyl-2-hexenoate (6d).** Aldehyde **4c**[18b] (100 mg, 0.52 mmol) was subjected to Wadsworth–Horner–Emmons olefination as described for **6a** with phosphonate **5a** (0.27 g, 1.0 mmol, 2.0 equiv) and freshly prepared LDA (0.78 mL, 1.0 M in THF, 0.78 mmol, 1.5 equiv) in THF (5 mL) under N_2 at −78 °C for 1 h. Purification by flash chromatography (1.4 × 28 cm silica gel, 20% EtOAc/hexanes) afforded a separable mixture of olefins (*E*)-**6d** and (*Z*)-**6d** (122 mg combined, 73%) as colorless oils. Pure (*E*)-**6d** was characterized: ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5 H, ArH), 6.84 (br s, 1 H, NH), 6.65 (br d, *J* = 9.6 Hz, 1 H, C=C*H*), 4.56 (dd, *J* = 9.6, 6.2 Hz, 1 H, C*H*OCH_2Ph), 4.46 (AB q, *J* = 12.0 Hz, $\Delta\nu$ = 72.8 Hz, 2 H, OCH_2Ph), 3.71 (s, 6 H, CO_2CH_3), 1.85 (dq, *J* = 6.7, 6.2 Hz, 1 H, C*H*$(CH_3)_2$), 0.98 and 0.91 (2 d, *J* = 6.7 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 154.2, 138.9, 129.6, 128.2, 127.7, 127.3, 126.8, 79.2, 70.7, 52.4, 52.4, 33.6, 18.6, 18.4; IR (neat) ν_{max} 3333, 1733, 1241, 769, 739, 697 cm^{-1}; EIMS, *m/z* (rel inten) 321 (M^+, 1), 278 (27), 246 (10), 218 (15), 91 (base); HRMS, *m/z* calcd for $C_{17}H_{23}NO_5$ 321.1576, found 321.1577. Pure (*Z*)-**6d** was characterized: ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5 H, ArH), 6.46 (br s, 1 H, NH), 6.35 (d, *J* = 8.4 Hz, 1 H, C=C*H*), 4.45 (AB q, *J* = 11.9 Hz, $\Delta\nu$ = 55.3 Hz, 2 H, OCH_2Ph), 3.96 (dd, *J* = 8.4, 6.2 Hz, 1 H, C*H*OCH_2Ph), 3.78 (s, 3 H, CO_2CH_3), 3.67 (s, 3 H, CO_2CH_3), 1.91 (dq, *J* = 6.8, 6.2 Hz, 1 H, C*H*$(CH_3)_2$), 0.97 and 0.91 (2 d, *J* = 6.8 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 154.8, 138.3, 133.1, 128.8, 128.3, 127.8, 127.6, 79.6, 71.2, 52.7, 52.6, 32.7, 18.4, 18.2; IR (neat) ν_{max} 3313, 1723, 1241, 774, 739, 697 cm^{-1}; EIMS, *m/z* (rel inten) 321 (M^+, 1), 278 (28), 246 (18), 218 (21), 91 (base); HRMS, *m/z* calcd for $C_{17}H_{23}NO_5$ 321.1576, found 321.1573.

(4*R)-Methyl 2-(*N*-Benzoylamino)-4-(benzyloxy)-5-methyl-2-hexenoate (6e).** Aldehyde **4c** (0.32 g, 1.7 mmol) was subjected to Wadsworth–Horner–Emmons olefination as described for **6a** with phosphonate **5b** (0.65 g, 2.2 mmol, 1.3 equiv) and freshly prepared LDA (2.0 mL, 1.0 M in THF, 2.0 mmol, 1.2 equiv) in THF (15 mL) under N_2 at −78 → 24 °C for 4 h. Purification of the residue by flash chromatography (1.4 × 25 cm silica gel, 20% EtOAc/hexanes) afforded a separable mixture of olefins (*E*)-**6e** and (*Z*)-**6e** (0.58 g combined, 95%) as a colorless

(18) (a) Compounds **4a** and **4b** were synthesized from (*S*)-(−)-ethyl lactate (Aldrich) by the following general reaction sequence: (1) NaH, THF, 0 °C, 15 min; *t*-$BuMe_2SiCl$ or cat. *n*-Bu_4NI, $PhCH_2Br$, 0 → 24 °C, 30 min, 75 and 72%, respectively; (2) *i*-Bu_2AlH, −78 °C, hexane/Et_2O, 84 and 97%, respectively. See also: Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768. Heathcock, C. H.; Kiyooka, S.-i.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. Mislow, K.; O'Brien, R. E.; Schaefer, H. *J. Am. Chem. Soc.* **1962**, *84*, 1940. Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180. (b) Compound **4c** was synthesized from (±)-2-hydroxy-3-methylbutyric acid (Aldrich) by the following reaction sequence: (1) CH_2N_2, Et_2O, 24 °C, 93%; (2) NaH, THF, 0 °C, 15 min; $PhCH_2Br$, cat. *n*-Bu_4NI, 0 → 24 °C, 30 min, 88%; (3) $LiAlH_4$, THF, 0 °C, 2 h, 92%; (4) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → 0 °C, 91%. For an alternative reaction sequence, see: McGarvey, G. J.; Kimura, M.; Kucerovy, A. *Tetrahedron Lett.* **1985**, *26*, 1419.

oil. Pure (*E*)-**6e** was characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (br s, 1 H, NH), 7.83 (m, 2 H, ArH), 7.56–7.43 (m, 3 H, ArH), 7.32–7.23 (m, 5 H, ArH), 7.18 (d, J = 9.6 Hz, 1 H, C=C*H*), 4.62 (dd, J = 9.6, 6.2 Hz, 1 H, C*H*OCH$_2$Ph), 4.52 (AB q, J = 12.1 Hz, $\Delta\nu$ = 75.0 Hz, 2 H, OC*H*$_2$Ph), 3.77 (s, 3 H, CO_2CH_3), 1.91 (dq, J = 6.7, 6.2 Hz, 1 H, C*H*(CH$_3$)$_2$), 1.02 and 0.95 (2 d, J = 6.7 Hz, 6 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 164.8, 138.9, 134.5, 132.0, 131.8, 128.8, 128.2, 127.8, 127.3, 127.0, 126.9, 79.4, 70.8, 52.6, 33.6, 18.7, 18.4; IR (neat) ν_{max} 3282, 1733, 1656, 1641, 1369, 1062, 697 cm^{-1}; EIMS, m/z (rel inten) 367 (M$^+$, 1), 324 (36), 276 (10), 206 (18), 105 (base), 91 (80); HRMS, m/z calcd for $C_{22}H_{25}NO_4$–C_3H_7 324. 1236, found 324.1231. Pure (*Z*)-**6e** was characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (br s, 1 H, NH), 7.60 (m, 1 H, ArH), 7.45 (m, 2 H, ArH), 7.30 (m, 7 H, ArH), 6.26 (d, J = 7.0 Hz, 1 H, C=C*H*), 4.53 (AB q, J = 11.4 Hz, $\Delta\nu$ = 28.8 Hz, 2 H, OC*H*$_2$Ph), 4.03 (dd, J = 7.0, 5.9 Hz, 1 H, C*H*OCH$_2$Ph), 3.79 (s, 3 H, CO_2CH_3), 2.01 (dq, J = 6.8, 5.9 Hz, 1 H, C*H*(CH$_3$)$_2$), 0.98 and 0.95 (2 d, J = 6.8 Hz, 6 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 165.0, 137.9, 132.1, 130.0, 128.9, 128.6, 128.0, 127.9, 127.4, 81.2, 71.7, 52.6 32.6, 18.3, 18.2; IR (neat) ν_{max} 3303, 1728, 1656, 1246, 733, 697 cm^{-1}; EIMS, m/z (rel inten) 367 (M$^+$, 1), 324 (12), 259 (14), 216 (55), 105 (base), 91 (38); HRMS, m/z calcd for $C_{22}H_{25}NO_4$–C_3H_7 324.1236, found 324.1231.

(2*Z*,4*S*) Methyl 4-Acetoxy-2-[*N*-(methoxycarbonyl)amino]-2-pentenoate (6f). A solution of silyl ether (*Z*)-**6a** (42 mg, 0.13 mmol) in THF (5 mL) under N_2 was treated with *n*-Bu$_4$NF (0.14 mL, 1.0 M in THF, 0.14 mmol, 1.05 equiv) at 0 °C and the reaction mixture was stirred for 5 min. The reaction was quenched by the addition of water (5 mL) and was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (10 mL) and were dried ($MgSO_4$) and concentrated *in vacuo* to provide a colorless oil. Purification by flash chromatography (0.9 × 15 cm silica gel, 50% EtOAc/hexanes) afforded the pure alcohol (21 mg, 78%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (br s, 1 H, NH), 6.41 (dd, J = 9.2, 0.3 Hz, 1 H, C=C*H*), 4.47 (dq, J = 9.2, 6.3 Hz, 1 H, C*H*CH$_3$), 3.76 (s, 3 H, CO_2CH_3), 3.70 (s, 3 H, CO_2CH_3), 1.26 (d, J = 6.3 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 156.3, 136.7, 125.3, 63.6, 53.5, 53.1, 22.1; IR (neat) ν_{max} 3323, 1713, 1241 cm^{-1}; EIMS, m/z (rel inten) 203 (M$^+$, 3), 188 (15), 171 (50), 160 (41), 144 (25), 128 (96), 112 (32), 100 (45), 84 (66), 62 (base); HRMS, m/z calcd for $C_8H_{13}NO_5$ 203.0794, found 203.0789.

A solution of the above alcohol (87 mg, 0.42 mmol) in THF (4 mL) at 24 °C under N_2 was treated with Ac_2O (59 μL, 0.62 mmol, 1.5 equiv) and a catalytic amount of NaOAc and *N*,*N*-(dimethylamino)pyridine (DMAP). The reaction mixture was stirred for 1.5 h and was quenched by the addition of 5% aqueous HCl (5 mL). EtOAc (10 mL) was added and the aqueous layer was extracted by EtOAc (2 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL) and were dried ($MgSO_4$) and concentrated *in vacuo* to provide a colorless oil. The residue was purified by flash chromatography (0.9 × 15 cm silica gel, 20–30% EtOAc/hexanes) to afford olefin (*Z*)-**6f** (82 mg, 80%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (br s, 1 H, NH), 6.00 (dd, J = 9.6, 0.7 Hz, 1 H, C=C*H*), 5.38 (dq, J = 9.6, 6.4 Hz, 1 H, C*H*CH$_3$), 3.74 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, CO_2CH_3), 1.99 (s, 3 H, CH_3CO), 1.36 (d, J = 6.4 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 164.8, 154.7, 129.2, 128.8, 67.0, 52.7, 52.6, 21.0, 19.4; IR (neat) ν_{max} 3328, 1732, 1239 cm^{-1}; EIMS, m/z (rel inten) 245 (M$^+$, 20), 202 (45), 186 (26), 171 (79), 154 (58), 128 (59), 82 (base); HRMS, m/z calcd for $C_{10}H_{15}NO_6$ 245.0899, found 245.0901.

General Procedure for the Preparation of α-Bromo Imines. (3*S*,4*S*)-Methyl 3-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-[*N*-(methoxycarbonyl)imino]pentanoate (7a). A solution of (*Z*)-**6a** (170 mg, 0.54 mmol) in $CDCl_3$ (0.5 mL) in an NMR tube under Ar was treated with *N*-bromosuccinimide (95 mg, 0.54 mmol) at 24 °C, and the contents were mixed by inverting the tube 20 times. The *N*-bromosuccinimide required approximately 15 min to dissolve completely and the reaction was monitored by ^{1}H NMR until judged to be complete. After 1 h at 24 °C, analysis by ^{1}H NMR showed a 5.3:1 mixture of *syn*- and *anti*-α-bromo imines **7a**. The solvent was evaporated *in vacuo* and the yellow oily residue was purified directly by flash chromatography (0.9 × 18 cm silica gel, 10% EtOAc/hexanes) to afford pure *syn*-**7a** (120 mg, 57%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (br d, J = 8.1 Hz, 1 H, C*H*Br), 4.39 (m, 1 H, C*H*CH$_3$), 3.86 (s, 3 H, CO_2CH_3), 3.85 (s, 3 H, CO_2CH_3), 1.42 (d, J = 6.0 Hz, 3 H, CHC*H*$_3$), 0.81 (s, 9 H, SiC(CH$_3$)$_3$), 0.06 and 0.01 (2 s, 6 H, Si(CH$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 159.1, 158.8, 70.1, 53.6, 53.5, 51.6, 25.6, 22.0, 17.8, –4.2, –5.1; IR (neat) ν_{max} 3416, 1740, 1236, 829, 778 cm^{-1}.

(3*S*,4*S*)-Methyl 4-(Benzyloxy)-3-bromo-2-[*N*-(methoxycarbonyl)imino]pentanoate (7b). Olefin (*Z*)-**6b** (190 mg, 0.65 mmol) in CH_2Cl_2 (3 mL) under N_2 was treated with *N*-bromosuccinimide (151 mg, 0.65 mmol) at 24 °C and was stirred for 3.5 h. The solvent was evaporated *in vacuo* and the yellow residue was purified by flash chromatography (1.4 × 20 cm silica gel, 10–20% EtOAc/hexanes) to afford pure *syn*-α-bromo imine **7b** (130 mg, 54%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 5 H, ArH), 4.84 (d, J = 8.5 Hz, 1 H, C*H*Br), 4.52 (AB q, J = 11.0 Hz, $\Delta\nu$ = 28.3 Hz, 2 H, OC*H*$_2$Ph), 4.14 (dq, J = 8.5, 6.1 Hz, 1 H, C*H*CH$_3$), 3.88 (s, 3 H, CO_2CH_3), 3.78 (s, 3 H, CO_2CH_3), 1.47 (d, J = 6.1 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 158.7, 158.4, 137.4, 128.3, 128.1, 127.8, 75.8, 72.1, 53.6, 53.5, 49.3, 17.7; IR (neat) ν_{max} 1736, 1238, 842, 744, 699 cm^{-1}; EIMS, m/z (rel inten) 371 (M$^+$, 1), 292 (4), 186 (62), 154 (59), 122 (21), 91 (base); HRMS, m/z calcd for $C_{15}H_{18}NO_5{}^{79}Br$ 371.0368, found 371.0370.

Pure *anti*-**7b** was obtained by the following procedure: olefin (*Z*)-**6b** (0.62 g, 2.1 mmol) in CH_2Cl_2 (5 mL) under N_2 was treated with *N*-bromosuccinimide (0.38 g, 2.1 mmol) at 24 °C and was stirred for 30 min. The solvent was evaporated *in vacuo* and the yellow residue was purified by flash chromatography using solvents, silica gel, and glassware that were cooled in a –20 °C freezer for 2 h prior to use. Flash chromatography (1.4 × 15 cm silica gel, 20% EtOAc/hexanes, 10 cm/min eluant flow rate) afforded pure *anti*-α-bromo imine **7b** (35 mg, 4%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.24 (m, 5 H, ArH), 4.97 (br d, J = 7.6 Hz, 1 H, C*H*Br), 4.63 (AB q, J = 11.3 Hz, $\Delta\nu$ = 14.8 Hz, 2 H, OC*H*$_2$Ph), 4.10 (dq, J = 7.6, 6.4 Hz, 1 H, C*H*CH$_3$), 3.86 (s, 3 H, CO_2CH_3), 3.81 (s, 3 H, CO_2CH_3), 1.32 (d, J = 6.4 Hz, 3 H, CHC*H*$_3$); EIMS, m/z (rel inten) 371 (M$^+$, 1), 292 (4), 186 (53), 154 (46), 122 (15), 91 (base); HRMS, m/z calcd for $C_{15}H_{18}NO_5{}^{79}Br$ 371.0368, found 371.0361.

(3*S*,4*S*)-Methyl 2-(*N*-benzoylimino)-4-(benzyloxy)-3-bromopentanoate (7c): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.78 (m, 2 H, ArH), 7.50 (m, 1 H, ArH), 7.33 (m, 2 H, ArH), 7.30–7.23 (m, 5 H, ArH), 4.92 (d, J = 8.6 Hz, 1 H, C*H*Br), 4.56 (AB q, J = 11.3 Hz, $\Delta\nu$ = 47.0 Hz, 2 H, OC*H*$_2$Ph), 4.28 (dq, J = 8.6, 6.1 Hz, 1 H, C*H*CH$_3$), 3.67 (s, 3 H, CO_2CH_3), 1.53 (d, J = 6.1 Hz, 3 H, CHC*H*$_3$).

(3*S,4*R**)-Methyl 4-(benzyloxy)-3-bromo-2-[*N*-(methoxycarbonyl)imino]-5-methylhexanoate (7d):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.21 (m, 5 H, ArH), 4.91 (d, J = 9.9 Hz, 1 H, C*H*Br), 4.60 (AB q, J = 10.6 Hz, $\Delta\nu$ = 66.1 Hz, 2 H, OC*H*$_2$Ph), 4.05 (dd, J = 9.9, 2.0 Hz, 1 H, C*H*OCH$_2$Ph), 3.86 (s, 3 H, CO_2CH_3), 3.77 (s, 3 H, CO_2CH_3), 2.39 (dq, J = 6.9, 2.0 Hz, 1 H, C*H*(CH$_3$)$_2$), 1.10 and 0.96 (2 d, J = 6.9 Hz, 6 H, CH(C*H*$_3$)$_2$).

(3*S,4*R**)-Methyl 2-(*N*-benzoylimino)-4-(benzyloxy)-3-bromo-5-methylhexanoate (7e):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (br s, 1 H, NH), 7.85 (m, 2 H, ArH), 7.54 (m, 1 H, ArH), 7.41 (m, 2 H, ArH), 7.32–7.21 (m, 5 H, ArH), 5.02 (d, J = 9.9 Hz, 1 H, C*H*Br), 4.70 (AB q, J = 10.7 Hz, $\Delta\nu$ = 55.7 Hz, 2 H, OC*H*$_2$Ph), 4.21 (dd, J = 9.9, 2.3 Hz, 1 H, C*H*OCH$_2$Ph), 3.68 (s, 3 H, CO_2CH_3), 2.46 (dq, J = 6.9, 2.3 Hz, 1 H, C*H*(CH$_3$)$_2$), 1.15 and 1.02 (2 d, J = 6.9 Hz, 6 H, CH(C*H*$_3$)$_2$).

General Procedure for the Preparation of Kinetic *E*-Vinyl Bromides. (2*E*,4*S*)-Methyl 4-(Benzyloxy)-3-bromo-2-[*N*-(methoxycarbonyl)amino]-2-pentenoate (8b). A solution of (*Z*)-**6b** (160 mg, 0.55 mmol) in $CDCl_3$ (2.5 mL) under Ar was treated with *N*-bromosuccinimide (97 mg, 0.55 mmol) at 24 °C, and the contents were mixed immediately by inverting the tube 20 times. The *N*-bromosuccinimide required approximately 15 min to dissolve completely and the reaction was monitored by ^{1}H NMR until judged to be complete. After 2 h at 24 °C, analysis by ^{1}H NMR showed an approximately 3:1 *syn*/*anti* mixture of α-bromo imines **7b**. The reaction mixture was cooled to –20 °C and 2,2,6,6-tetramethylpiperidine (92 μL, 0.55 mmol) was added and the tube was again inverted 20 times. After 5 d at –20 °C, analysis by ^{1}H NMR revealed a 6.7:1 mixture of olefins (*E*)- and

(*Z*)-**8b**. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (1.4 × 20 cm silica gel, 20% EtOAc/hexanes) to afford pure (*E*)-**8b** (160 mg, 79%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (br s, 1 H, NH), 7.32 (m, 5 H, ArH), 4.52 (AB q, J = 11.6 Hz, $\Delta\nu$ = 110.5 Hz, 2 H, OCH_2Ph), 4.32 (br q, J = 6.5 Hz, 1 H, $CHCH_3$), 3.86 (s, 3 H, CO_2CH_3), 3.66 (s, 3 H, CO_2CH_3), 1.40 (d, J = 6.5 Hz, 3 H, $CHCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 153.4, 137.1, 129.9, 129.0, 128.6, 128.6, 114.1, 79.0, 71.7, 53.4, 53.1, 19.3; IR (neat) ν_{max} 3317, 1740, 1497, 1239, 738, 700 cm^{-1}; EIMS, m/z (rel inten) 371/373 (M^+, 3/3), 292 (14), 234 (11), 184 (82), 91 (base); HRMS, m/z calcd for $C_{15}H_{18}NO_5{}^{79}Br$ 371.0368, found 371.0378.

General Procedure for the Preparation of Thermodynamic *Z*-Vinyl Bromides. (2*Z*,4*S*)-Methyl 4-(Benzyloxy)-3-bromo-2-[*N*-(methoxycarbonyl)amino]-2-pentenoate (8b). A solution of (*Z*)-**6b** (170 mg, 0.58 mmol) in $CDCl_3$ (2.7 mL) under Ar was treated with *N*-bromosuccinimide (103 mg, 0.58 mmol) at 24 °C, and the contents were mixed immediately by inverting the tube 20 times. The *N*-bromosuccinimide required approximately 15 min to dissolve completely and the reaction was monitored by ^{1}H NMR until judged to be complete. After 1.5 h at 24 °C, analysis by ^{1}H NMR showed an approximately 3:1 *syn/anti* mixture of α-bromo imines **7b**. DABCO (65 mg, 0.58 mmol) was added and the tube was again inverted 20 times. After 32 h at 24 °C, the solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (1.4 × 20 cm silica gel, 20% EtOAc/hexanes) to afford (*Z*)-**8b** (155 mg, 72%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H, ArH), 6.70 (br s, 1 H, NH), 4.41 (br q, J = 6.2 Hz, 1 H, $CHCH_3$), 4.38 (AB q, J = 11.9 Hz, $\Delta\nu$ = 78.5 Hz, 2 H, OCH_2Ph), 3.74 (s, 3 H, CO_2CH_3), 3.74 (s, 3 H, CO_2CH_3), 1.35 (d, J = 6.2 Hz, 3 H, $CHCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 153.4, 137.7, 129.6, 128.4, 127.9, 127.7, 123.9, 72.4, 70.2, 53.2, 53.0, 21.1; IR (neat) ν_{max} 3325, 1732, 1489, 700 cm^{-1}; EIMS, m/z (rel inten) 371 (M^+, 1), 292 (20), 184 (48), 154 (31), 91 (base); HRMS, m/z calcd for $C_{15}H_{18}NO_5{}^{79}Br$ 371.0368, found 371.0364.

(4*S*)-Methyl 3-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-[*N*-(methoxycarbonyl)amino]-2-pentenoate (8a). Pure (*E*)-**8a** was characterized: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (br s, 1 H, NH), 4.52 (br q, J = 6.4 Hz, 1 H, $CHCH_3$), 3.78 (s, 3 H, CO_2CH_3), 3.63 (s, 3 H, CO_2CH_3), 1.34 (d, J = 6.4 Hz, 3 H, $CHCH_3$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.06 and 0.06 (2 s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 153.2, 129.6, 112.0, 75.9, 53.2, 52.9, 26.0, 21.8, 18.4, -4.8, -4.9; IR (neat) ν_{max} 3339, 2947, 1741, 1486, 1232, 833, 782 cm^{-1}; EIMS, m/z (rel inten) 395/397 (M^+, 5/5), 338/340 (84/84), 306/308 (81/81), 278/280 (40/40), 258 (31), 184 (37), 75 (base); HRMS, m/z calcd for $C_{14}H_{26}NO_5Si^{79}Br$ 395.0763, found 395.0759. Pure (*Z*)-**8a** was characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (br s, 1 H, NH), 4.81 (br q, J = 6.1 Hz, 1 H, $CHBr$), 3.85 (s, 3 H, CO_2CH_3), 3.75 (s, 3 H, CO_2CH_3), 1.27 (d, J = 6.1 Hz, 3 H, $CHCH_3$), 0.83 (s, 9 H, $SiC(CH_3)_3$), -0.01 and -0.02 (2 s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 153.7, 126.4, 66.7, 53.1, 52.9, 25.7, 23.8, 18.1, -5.0, -5.1; IR (neat) ν_{max} 3415, 1739, 1632, 833 cm^{-1}; CIMS, m/z (rel inten) 338/340 ($M^+-C_4H_9$, 36/36), 306/308 (15/15), 264/266 (14/14), 258 (base); HRMS, m/z calcd for $C_{14}H_{26}NO_5Si^{79}Br-C_4H_9$ 338.0059, found 338.0042.

(4*S*)-Methyl 2-(*N*-Benzoylamino)-4-(benzyloxy)-3-bromo-2-pentenoate (8c). Pure (*E*)-**8c** was characterized: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (br s, 1 H, NH), 7.43 (m, 3 H, ArH), 7.41-7.31 (m, 5 H, ArH), 7.25-7.20 (m, 2 H, ArH), 4.64 (AB q, J = 10.9 Hz, $\Delta\nu$ = 25.3 Hz, 2 H, OCH_2Ph), 4.45 (q, J = 6.6 Hz, 1 H, $CHCH_3$), 3.92 (s, 3 H, CO_2CH_3), 1.50 (d, J = 6.6 Hz, 3 H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 163.3, 136.2, 132.3, 131.9, 130.2, 128.8, 128.6, 128.6, 127.3, 112.4, 102.9, 81.5, 72.1, 52.8, 18.8; IR (neat) ν_{max} 3313, 1733, 1662, 1472, 739, 697 cm^{-1}; EIMS, m/z (rel inten) 417/419 (M^+, 1/1), 338 (6), 230 (32), 105 (base), 91 (45), 77 (58); HRMS, m/z calcd for $C_{20}H_{20}NO_4{}^{79}Br$ 417.0576, found 417.0579. Pure (*Z*)-**8c** was characterized: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (br s, 1 H, NH), 7.86 (m, 2 H, ArH), 7.59 (m, 1 H, ArH), 7.49 (m, 2 H, ArH), 7.34-7.23 (m, 5 H, ArH), 4.53 (q, J = 6.2 Hz, 1 H, $CHCH_3$), 4.44 (AB q, J = 11.9 Hz, $\Delta\nu$ = 75.9 Hz, 2 H, OCH_2Ph), 3.79 (s, 3 H, CO_2CH_3), 1.40 (d, J = 6.2 Hz, 3 H, $CHCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 163.2, 138.1, 133.2, 132.7, 130.2, 129.4, 128.8, 128.3, 128.1, 127.8, 126.4, 72.7, 70.7, 53.5, 21.6; IR (neat) ν_{max} 3245, 1727, 1639, 1305, 723, 688 cm^{-1}; EIMS, m/z (rel inten) 417/419 (M^+, 1/1), 338 (21), 230 (74), 198 (28), 105 (base), 91 (81), 77 (75); HRMS, m/z calcd for $C_{20}H_{20}NO_4{}^{79}Br$ 417.0576, found 417.0562.

(4*R)-Methyl 4-(Benzyloxy)-3-bromo-2-[*N*-(methoxycarbonyl)amino]-5-methyl-2-hexenoate (8d).** Following the bromination procedure described for the preparation of (*E*)-**8b**, olefin (*Z*)-**6d** (100 mg, 0.31 mmol), *N*-bromosuccinimide (55 mg, 0.31 mmol), and TMP (53 μL, 0.31 mmol) under Ar afforded approximately a 7.6:1 mixture of olefins (*E*)- and (*Z*)-**8d** after 11 d at -20 °C. The mixture was purified by flash chromatography (1.4 × 20 cm silica gel, 20% EtOAc/hexanes) to afford pure (*E*)-**8d** (83 mg, 66%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (br s, 1 H, NH), 7.32 (m, 5 H, ArH), 4.53 (AB q, J = 11.6 Hz, $\Delta\nu$ = 152.4 Hz, 2 H, OCH_2Ph), 3.86 (s and d, J = 7.1 Hz, 4 H, overlapping CO_2CH_3 and $CHOCH_2Ph$), 3.64 (s, 3 H, CO_2CH_3), 2.09 (apparent septet, J = 6.8 Hz, 1 H, $CH(CH_3)_2$), 0.99 and 0.94 (2 d, J = 6.8 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 153.3, 137.0, 131.4, 128.9, 128.8, 128.6, 111.0, 88.4, 72.3, 53.3, 53.0, 32.3, 19.5, 18.7; IR (neat) ν_{max} 3333, 1739, 1641, 1487, 1236, 738, 697 cm^{-1}; EIMS, m/z (rel inten) 399/401 (M^+, 3/3), 356/358 (12/12), 296 (16/169), 180 (13), 91 (base); HRMS, m/z calcd for $C_{17}H_{22}NO_5{}^{79}Br$ 399.0681, found 399.0677. Following the bromination procedure described for the preparation of (*Z*)-**8b**, olefin (*Z*)-**6d** (145 mg, 0.45 mmol), *N*-bromosuccinimide (80 mg, 0.45 mmol), and DABCO (51 mg, 0.45 mmol) under Ar afforded approximately a 1:6.5 mixture of olefins (*E*)- and (*Z*)-**8d** after extended exposure to base. The mixture was purified by flash chromatography (1.4 × 20 cm silica gel, 20% EtOAc/hexanes) to afford pure (*Z*)-**8d** (133 mg, 73%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5 H, ArH), 6.81 (br s, 1 H, NH), 4.41 (AB q, J = 11.9 Hz, $\Delta\nu$ = 86.1 Hz, 2 H, OCH_2Ph), 3.80 (br d, J = 9.1 Hz, 1 H, $CHOCH_2Ph$), 3.75 (s, 3 H, CO_2CH_3), 3.74 (s, 3 H, CO_2CH_3), 1.98 (m, 1 H, $CH(CH_3)_2$), 1.05 (d, J = 6.5 Hz, 3 H, $CH(CH_3)_2$), 0.78 (d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 153.4, 138.0, 130.9, 128.3, 127.9, 127.6, 121.4, 82.6, 70.4, 53.2, 52.9, 32.4, 19.4, 18.4; IR (neat) ν_{max} 3323, 1739, 1631, 1487, 739, 697 cm^{-1}; CIMS (NH_3), m/z (rel inten) 417/419 ($M^+ + NH_4$, 38/38), 385/387 (20/20), 368/370 (31/31), 292/294 (base), 260/262 (50/50), 216 (83), 182 (46), 156 (44), 108 (71); HRMS, m/z calcd for $C_{17}H_{22}NO_5{}^{79}Br-C_3H_7$: 356.0134; found: 356.0134.

(4*R)-Methyl 2-(*N*-Benzoylamino)-4-(benzyloxy)-3-bromo-5-methyl-2-hexenoate (8e).** Pure (*E*)-**8e** was characterized: mp 153.5-155 °C ($Et_2O/CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (br s, 1 H, NH), 7.42 (m, 3 H, ArH), 7.35 (m, 2 H, ArH), 7.30 (m, 3 H, ArH), 7.22 (m, 2 H, ArH), 4.66 (AB q, J = 10.9 Hz, $\Delta\nu$ = 82.7 Hz, 2 H, OCH_2Ph), 4.07 (d, J = 6.2 Hz, 1 H, $CHOCH_2Ph$), 3.92 (s, 3 H, CO_2CH_3), 2.17 (dq, J = 6.8, 6.2 Hz, 1 H, $CH(CH_3)_2$), 1.06 and 1.02 (2 d, J = 6.8 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 163.4, 136.6, 132.6, 132.3, 131.9, 129.1, 129.0, 129.0, 128.9, 127.6, 110,6, 90.8, 73.4, 53.1, 32.7, 19.9, 18.4; IR (KBr) ν_{max} 3324, 1726, 1661, 1276, 1072, 743, 702 cm^{-1}; EIMS, m/z (rel inten) 445/447 (M^+, 3/3), 402/404 (15/15), 258/260 (10/10), 226 (9), 105 (84), 91 (base); HRMS, m/z calcd for $C_{22}H_{24}NO_4{}^{79}Br$ 445.0889, found 445.0904. Pure (*Z*)-**8e** was characterized: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (br s, 1 H, NH), 7.87 (m, 2 H, ArH), 7.58 (m, 1 H, ArH), 7.49 (m, 2 H, ArH), 7.37-7.23 (m, 5 H, ArH), 4.47 (AB q, J = 11.9 Hz, $\Delta\nu$ = 135.5 Hz, 2 H, OCH_2Ph), 3.92 (d, J = 9.2 Hz, 1 H, $CHOCH_2Ph$), 3.80 (s, 3 H, CO_2CH_3), 2.02 (dq, J = 9.2, 6.7 Hz, 1 H, $CH(CH_3)_2$), 1.08 and 0.83 (2 d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 163.3, 138.4, 133.2, 132.7, 131.5, 129.4, 128.7, 128.4, 128.0, 127.9, 124.6, 82.9, 70.9, 53.4, 32.9, 19.8, 18.8; IR (neat) ν_{max} 3404, 3324, 1733, 1675, 1472, 1297, 1058, 702 cm^{-1}; EIMS, m/z (rel inten) 445/447 (M^+, 1/1), 402/404 (19/19), 260 (8), 105 (80), 91 (base); HRMS, m/z calcd for $C_{22}H_{24}NO_4{}^{79}Br$ 445.0889, found 445.0878.

(4*S*)-Methyl 4-Acetoxy-3-bromo-2-[*N*-(methoxycarbonyl)amino]-2-pentenoate (8f). Pure (*E*)-**8f** was characterized: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (br s, 1 H, NH), 5.47 (q, J = 6.4 Hz, 1 H, $CHCH_3$), 3.81 (s, 3 H, CO_2CH_3), 3.69 (s, 3 H, CO_2CH_3), 2.07 (s, 3 H, CH_3CO), 1.43 (d, J = 6.4 Hz, 3 H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 164.5, 154.2, 131.6, 117.1, 69.0, 53.4, 53.0, 21.2, 19.7; IR (neat) ν_{max} 3313, 1739, 1492, 1246 cm^{-1}; CIMS (NH_3), m/z (rel inten) 341/343 ($M^+ + NH_4$, 10/10), 309/311 (6/6), 264/266 (95/95), 186 (base); HRMS, m/z calcd for

$C_{10}H_{14}NO_6{}^{79}Br-C_2H_3O_2$: 263.9871; found: 263.9861. Pure (*Z*)-**8f** was characterized: ^1H NMR (500 MHz, $CDCl_3$) δ 6.54 (br s, 1 H, NH), 5.83 (q, J = 6.4 Hz, 1 H, C*H*CH_3), 3.87 (s, 3 H, CO_2CH_3), 3.72 (s, 3 H, CO_2CH_3), 2.01 (s, 3 H, CH_3CO), 1.43 (d, J = 6.4 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 162.9, 153.8, 130.4, 68.5, 53.6, 53.5, 21.3, 20.0; IR (neat) ν_{max} 3313, 1739, 1631, 1231 cm^{-1}; CIMS (NH_3), m/z (rel inten) 341/343 (M^+ + NH_4, 4/4), 309/311 (8/8), 264/266 (40/40), 186 (base); HRMS, m/z calcd for $C_{10}H_{14}NO_6{}^{79}Br-{}^{79}Br$ 244.0821, found 244.0829.

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Supplementary Material Available: Photocopies of ^1H or ^{13}C NMR spectra of **6a–f**, **7a–f**, and **8a–f**, and general experimental procedures (57 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.