Engineering Acyclic Stereocontrol in the Alkylation of Vinylglycine-Derived Dianions: Asymmetric Synthesis of Higher α-Vinyl Amino Acids

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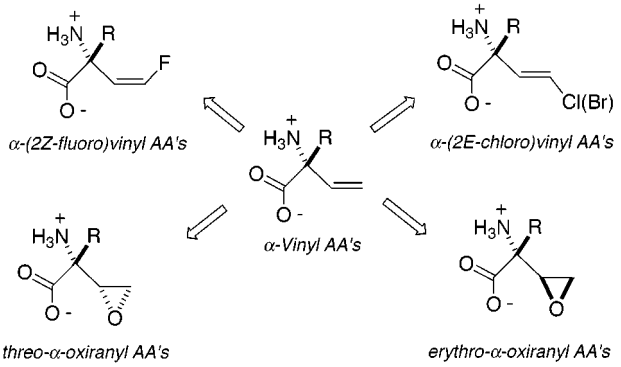
A generalizable synthesis of higher L-α-vinyl amino acids is presented. The strategy pursued here involves the introduction of the amino acid side chain via the alkylation of a chiral, vinylglycine-derived dianionic dienolate, bearing the (−)-8-(β-naphthyl)menthyl (d'Angelo) auxiliary. A model is presented that postulates a favored "exo-entended" conformation for this dienolate, leading to C_α-alkylation at the *si* face. The model invokes internal amidate chelation to control ester enolate geometry and soft−soft interactions between the polarizable β-naphthyl ring of the auxiliary and the extended π-system of the dienolate to shield the *re* face. Heats of formation for four conformers of this dianion were calculated for their semiempirical optimized geometries (PM3). The results support the notion that in these vinylglycine-derived dianionic dienolates, "exo" conformations are considerable lower in energy than their "endo" counterparts, with the "exo-entended" conformation being most favorable. In fact, the d'Angelo auxiliary gives a greater degree of acyclic stereocontrol in this system when compared with the (−)-8-phenylmenthyl (Corey) and *trans*-2-(β-naphthyl)-cyclohexyl auxiliaries, using isobutyl iodide and benzyl bromide as model electrophiles. These dianions are generated from the corresponding dehydrobutyrine esters via sequential deprotonation with LDA and *n*-BuLi (2 equiv). When alkylations are carried out at −78 °C in THF−HMPA, they proceed in 65−81% yields, with both regiocontrol (deconjugative α-alkylation is preferred over γ-alkylation) and a great degree of acyclic stereocontrol [91:9 to ≥98:2 diastereomeric ratios (10 examples)]. The auxiliary may be recovered in high yield (generally 90%) using a modification of Gassman's "anhydrous hydroxide" conditions, in which considerably higher temperatures are employed. Among the side chains introduced directly are those of butyrine, leucine, ornithine, phenylalanine, aspartate, valine, and norvaline. The lysine side chain is elaborated via a 4-step sequence from the alkylation product obtained with 1-chloro-4-iodobutane as electrophile. Importantly, to our knowledge, this work represents the first asymmetric synthesis of L-α-vinyl analogues of *m*-tyrosine, ornithine, and lysine, known time-dependent inhibitors for amino acid decarboxylases.

Introduction

Higher (R ≠ H) α-vinyl amino acids (AAs) are an especially versatile class of α-branched AAs. From the point of view of mechanism-based enzyme inactivation, the vinyl branch may serve as a masked trigger for the suicide inactivation of pyridoxal phosphate (PLP)-dependent enzymes, especially amino acid decarboxylases (AADCs).[1,2] For example, we have found that α-vinylarginine and α-vinyllysine are time-dependent inactivators of their cognate decarboxylases.[1] Perhaps, more importantly from our perspective, the vinyl branch also serves as a convenient synthetic precursor for the installation of other, previously unexplored, potential AADC "suicide triggers" along the α-branch (Scheme 1).[3] Since the amino acid R group is normally a key recognition element in the target AADC active site, this strategy is particularly advantageous. That is, from a given higher α-vinyl AA, one could generate an array of potential suicide substrates, all targeted at the same AADC active site. A general strategy for the enantioselective synthesis of higher α-vinyl AAs would then address the absolute stereochemical issue for the entire array. Herein, we provide one such solution, which is generalizable to some of the most biologically relevant R groups.

Scheme 1. α-Vinyl AAs: Versatile Intermediates for α-Branched AA Synthesis



It is important to point out that, in addition to these applications of free, monomeric α-branched AAs, there

(1) For a detailed discussion and set of references on uses of the α-vinyl trigger to inactivate pyridoxal phosphate (PLP) dependent enzymes, see: Berkowitz, D. B.; Jahng, W.-J.; Pedersen, M. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2151−2156.

(2) For elegant mechanistic work on the mode of actuation of a related vinyl trigger, see: Nanavati, S. M.; Silverman, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 9341−9349.

(3) (a) Berkowitz, D. B.; Jahng, W.-J. From α-Vinyl Amino Acids to Higher α-(2-Fluoro)vinyl Amino Acids; 215th National ACS Meeting, March 29−April 2, 1998; ORGN-336. (b) Berkowitz, D. B.; Pedersen, M. L.; Jahng, W.-J. *Tetrahedron Lett.* **1996**, *37*, 4309−4312. (c) Berkowitz, D. B.; Pedersen, M. L. *J. Org. Chem.* **1995**, *60*, 5368−5369.

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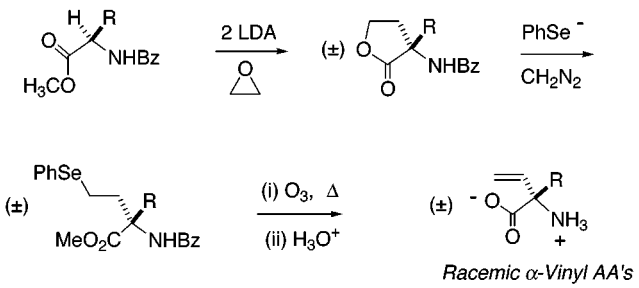
is also much current interest in the incorporation of α,α-disubstituted AAs into peptides and proteins. Among the properties that α-branched AAs confer upon their derivative peptides are the following: (i) α-helicity,[4a,d] (ii) 3_{10}-helicity,[4a−c,e] and (iii) resistance to proteolysis.[5,6] Of late, there have also been several creative approaches to the synthesis of libraries of α-branched AAs for combinatorial chemistry applications.[7] Moreover, the Schultz group has demonstrated that α-branched AAs may be quite efficiently inserted into specific positions in proteins of interest using chemically misacylated tRNA's under in vitro translation conditions.[8] These peptide/protein engineering applications have involved primarily simple α-alkyl AAs heretofore, most likely, due to synthetic accessibility.

Be the application enzyme inhibition, de novo peptide design, or total synthesis,[9] enantiomerically enriched α-vinyl AAs are desirable. Recent years have seen extensive activity in the enantioselective synthesis of α-methyl AAs.[10,11] By contrast, though several routes to optically enriched vinylglycine are available,[9d,12] asymmetric routes to higher α-vinyl amino acids are much more limited.[13] Seebach's pioneering self-reproduction of chirality approach (for α-vinylalanine,[13a] α-vinylbutyrine,[13a] and α-vinylphenylalanine[13b]) stands out in this regard. Other routes appear to be limited to α-vinylalanine so far. Hegedus has reported a synthesis of D-α-vinylalanine, building upon Ojima's chiral β-lactam-based technology.[13c] Frutos[13d] synthesized scalemic L-α-vinylalanine using the Beckmann rearrangement of the requisite *O*-tosyl oxime generated from the appropriate, enantiomeric β-ketoester.[13e] Petasis has recently described an elegant synthesis of related β,γ-unsaturated AAs via a Mannich-type condensation reaction involving alkenyl boronate, amine, and α-keto acid components.[14]

Scheme 2. Formal Vinylation of Amino Acids



Racemic α-Vinyl AA's

Results and Discussion

We described a convenient synthesis of racemic, α-vinyl AAs from the corresponding amino acids (Scheme 2)[15a] and the partial kinetic resolution of these via a lipase-mediated "reverse transesterification" procedure.[15b] Parallel to our enzymatic resolution studies, we undertook to develop asymmetric synthetic routes to the target unsaturated, α-branched analogues of naturally occurring α-AAs. It will be noted that our initial, "racemic" synthesis involved the formal vinylation of dianions derived from *N*-benzoyl-protected amino acid esters. Ethylene oxide served as a convenient and readily available vinyl cation equivalent.

We reasoned that it ought to be possible to fashion chiral versions of these amino acid-derived dianions[16] through the appendage of a chiral ester auxiliary and thereby develop an asymmetric version of this chemistry. In fact, attachment of the Corey auxiliary [(−)-8-phenylmenthol] through an ester linkage to the α-carboxyl group of *N*-benzoylalanine proved advantageous. Initial attempts to formally α-vinylate the resultant chiral dianion (**1**), with ethylene oxide as vinyl cation equivalent, including in the presence of $BF_3{\cdot}Et_2O$, led to complex

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(6) For example, a family of tripeptidic antithrombotic agents developed at Lilly contains a D-α-branched amino acid as an essential component: Sall, D. J.; Shuman, R. T.; Smith, G. F.; Wiley: M. R. U.S. Patent No. 5,484,772; July 16, 1996.

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(10) For reviews, see: (a) Seebach, D.; Sting, A. R.; Hoffman, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1650. (c) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, 1989.

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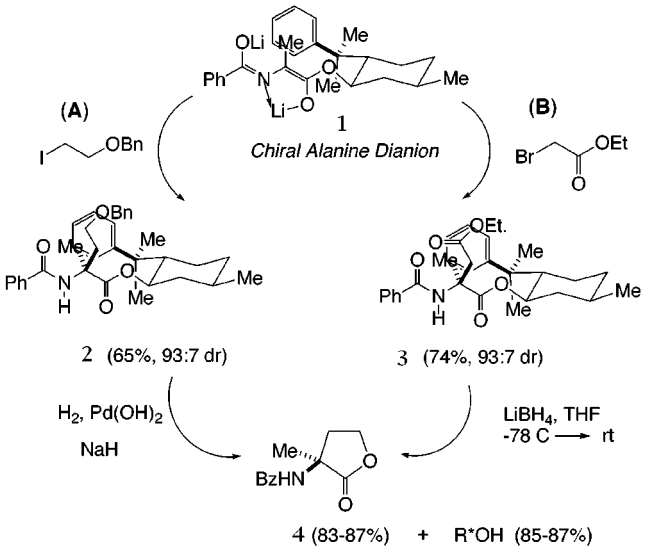
(14) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445−446.

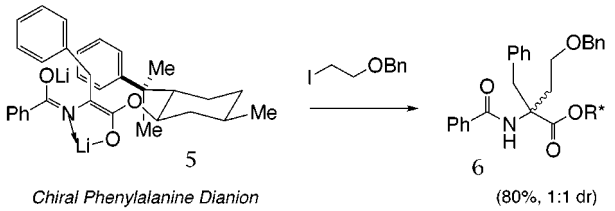
(15) (a) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966−6975. (b) Berkowitz, D. B.; Pumphrey, J. A.; Shen, Q. *Tetrahedron Lett.* **1994**, *35*, 8743−8747.

(16) (a) For the first work of which we are aware on chiral hippurate-derived dianions (modest diastereoselectivity), see: Davenport, K. G.; Mao, D. T.; Richmond, C. M.; Bergbreiter, D. E.; Newcomb, M. *J. Chem. Res., Synop.* **1984**, 148−149; *J. Chem. Res., Miniprint* 1518−1530. For more recent work on *N*-Boc AA-derived dianions as chiral glycine equivalents and on chiral, peptide-derived polyanions, see, respectively: (b) Studer, A.; Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1185−1205. (c) Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S.-i.; Wenger, R. *Helv. Chim. Acta* **1991**, *74*, 197−224.

Scheme 3. Alkylations Using Vinyl Cation Equivalents Equipped with Built-in Auxiliary Releases



Scheme 4



mixtures of products. Pleasingly, the alternative vinyl cation equivalents, ethyl bromoacetate and 2-iodoethyl benzyl ether,[17] were effectively coupled to dianion **1**, and with good diastereoselection (Scheme 3). Conveniently, as is the case for ethylene oxide, these electrophiles possess a built-in auxiliary release that can be actuated under reductive conditions. Thus, each approach formally gives D-α-vinylalanine in 86% ee.

Unfortunately, this strategy for engineering a chiral bias into such amino acid-derived dianions did not prove general. Thus, the analogous phenylalanine-derived chiral dianion (**5**) showed little to no diastereoselection in alkylation reactions (Scheme 4).

These dianions had been designed with two principal considerations. On one hand, it was expected that the α-benzamidate functionality would serve as an ideal ligand for the ester enolate lithium and thereby "lock" this enolate into the *E* geometry. Further, it was hypothesized that a favorable soft−soft (or dipole−induced dipole) interaction might be available between the polarizable aromatic ring in such 8-arylmenthyl-type auxiliaries and the π-system of the dianion. Provided that these interactions persist as the dianion interacts with the incoming alkyl halide and approaches the relevant transition state, alkylations would be expected to occur preferentially at the *si* face. From the results obtained here, one might postulate that the introduction of bulky substituents at the α-carbon (such as Bn, here, and many of the other natural AA side chains) has a disruptive effect on such interaction, and thereby compromises diastereoselection. On the other hand, were such side chains to be replaced with an unsubstituted vinyl group, the resulting dienolate π-surface would be extended by an additional two p-orbitals, and this might enhance interaction with the polarizable β-naphthyl group.[18] This line of reasoning led us to consider a converse synthetic strategy; namely, the α-alkylation of chiral vinylglycine-derived dianionic dienolates.

As a computational test of this working model for conformational control, we performed a series of semiempirical PM3[25] geometry optimizations upon the dianion derived from the 8-(β-naphthyl)menthyl (d'Angelo) auxiliary.[20a] Lithium was chosen as the counterion, given that, experimentally, the first deprotonation is with LDA and the second with butyllithium.[26] The degree of "hydration" (water molecules were used as THF/HMPA surrogates) was chosen as follows. Several iterations of geometry optimizations were performed, assuming chelation from the amidate nitrogen to the ester enolate lithium, and varying the numbers of waters per lithium.

(17) Liu, C.; Coward, J. K. *J. Med. Chem.* **1991**, *34*, 2094−2101.

(18) Face-to-face π−π interactions have been invoked to rationalize the conformational control obtained in systems where such arylmenthyl or arylcyclohexyl auxiliaries are appended to electron-deficient π-systems such as acrylates (in Diels−Alder or conjugate addition reactions) or glyoxylates (in oxy-ene or Grignard addition reactions).[19,20] As has been pointed out by Whitesell, examples of the inverse-electron demand situation are less common.[19c] However, systems have been described in which either an electron-rich silyl ketene acetal (hetero-Diels−Alder reaction),[21b] an α-alkoxy ester enolate (imine-ester enolate cyclocondensation reaction)[21c] or an AA-derived ester enolate (monoanion alkylation),[21a] bears a blocking group of the 8-arylmenthyl or 2-*trans*-arylcyclohexyl variety, and in which excellent stereocontrol is achieved. In these cases, models of the transition state assemblies have been formulated that correctly predict the sense of asymmetric induction observed and that, either explicitly or implicitly, invoke favorable π−π interactions[22] for conformational control. Nonetheless, such arguments remain controversial, particularly with systems in which one of the π-components is electron rich. Arguing against such interactions, several elegant model studies on neutral species support the notion that electrostatic forces dominate face-to-face π−π interactions.[23] In other model systems, however, it appears that dispersion forces can make significant contributions to such π−π interactions,[24] particularly when a highly polarizable fused aromatic ring is involved.[24b] In the case of the "exo-extended" dienolate working model presented here, it is conceivable that dispersion forces could lead to a favorable face-to-face interaction, particularly as the system approaches an alkylation transition state in which charge is becoming more widely dispersed.

(19) For a pioneering example of the use of the 8-phenylmenthyl auxiliary in an asymmetric Diels−Alder reaction, see: Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908−6909.

(20) For reviews on the postulated use of π−π interactions in asymmetric organic synthesis, see: (a) Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293−2304. (b) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475−497. (c) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953−964.

(21) (a) Meyer, L.; Poirier, J.-M.; Duhamel, P.; Duhamel, L. *J. Org. Chem.* **1998**, *63*, 8094−8095. (b) Swindell, C. S.; Tao, M. *J. Org. Chem.* **1993**, *58*, 5889−5891. (c) Ojima, I.; Habus, I.; Zhao, M.; George, G.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681−1683.

(22) For a general discussion on factors influencing π−π interactions, see: Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534.

(23) (a) Cozzi, F.; Cinquini, M.; Annuziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330−5331. (b) Muehldorf, A. V.; Van Engen D.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561−6562.

(24) (a) Williams, V. E.; Lemieux, R. P. *J. Am. Chem. Soc.* **1998**, *120*, 11311-11315. (b) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Parris, K.; Williams, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1082−1090.

(25) The MacSpartan Plus (version 1.1.9) package (Wavefunction, Inc., Irvine, CA 92612) was used for all geometry optimizations. Complete tables of atomic Cartesian coordinates, atomic partial charges, calculated dipole moments and heats of formation for each of the conformers **I**−**IV** are available upon request.

(26) Operationally, C_α-alkylations in these dianionic dienolate systems were found to be most successful if, following initial deprotonation with LDA, two equivalents of *n*-BuLi were employed for the second deprotonation. Presumably, the first equivalent of *n*-BuLi is required to deprotonate the diisopropylamine that is formed in the initial deprotonation reaction.

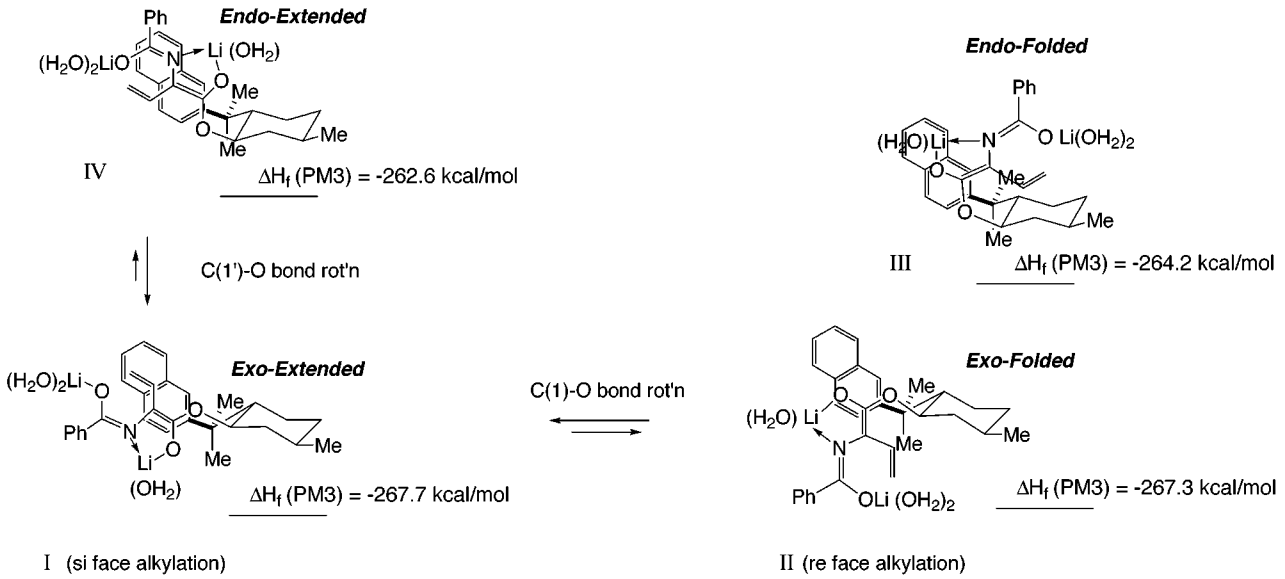


Figure 1. Displayed are the results of semiempirical geometry optimizations (PM3[25]) on rotamers of the vinylglycine-derived dienolate bearing the d'Angelo auxiliary. All conformers have 231 independent degrees of freedom, and 199 basis functions were used. Convergence was set at a 0.5 cal/mol energy differential between successive iterations and was achieved after 322, 352, 321, and 317 cycles for conformers **I**−**IV**, respectively.

We settled upon solvent coordination numbers of two for the amidate lithium, and one for the ester enolate lithium, in that optimized geometries appeared to permit one favorable cation-π interaction for each lithium center (vinyl group → amidate Li and phenyl group → enolate Li).

With this degree of solvent ligation, four local minima were found for the dianionic dienolate, differing primarily in dihedral angles with respect to rotations about the C(1′)-O bond ("exo" versus "endo" rotomers) and about the C(1)−O bond ("extended" vs "folded").[27] The two endo conformers are estimated to lie considerably higher in energy (3−5 kcal/mol in terms of calculated heats of formation; Figures 1 and 2) than their exo counterparts. To the extent that ground-state conformational preferences reflect dianion conformational preferences in the transition state for this reaction,[28] it would appear that exo-type conformations are greatly favored. Furthermore, there appears to be a slight preference for exo-extended conformer **I** over exo-folded conformer **II**, consistent with the preference for *si* face alkylation that is observed here (vide infra). In the PM3-optimized geometry for **I**, *re* face approach is effectively blocked as the atoms of the dienolate π-surface stretching from the bridging ester oxygen to the vinyl group [atoms O−C(1)−C(2)-C(3)−C(4)] are within 2.9−4.2 Å of the nearest carbons of the β-naphthyl group.[29]

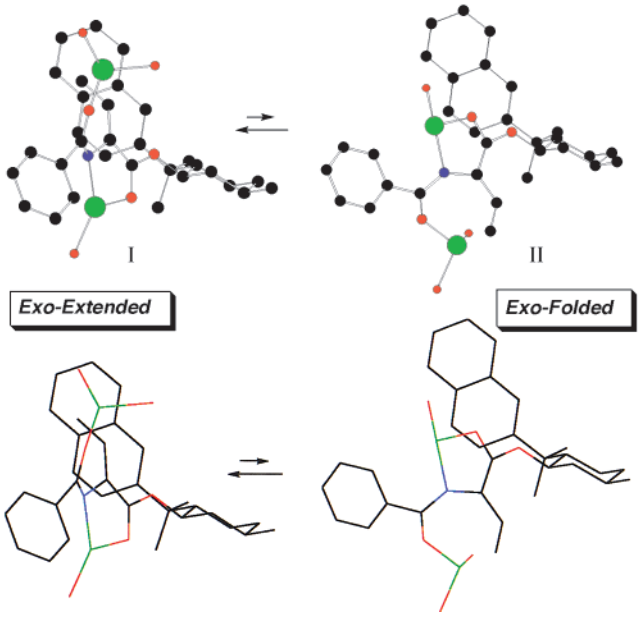


Figure 2. Shown is a three-dimensional view of the lowest energy exo conformers. Though modeling was carried out with all hydrogens in place, they have been omitted here for clarity. For the exo-entended conformer, the calculated partial charges for the C-atoms of the polarizable naphthyl blocking group are, from C(1″) to C(10″), respectively, as follows: −0.17; −0.05; −0.11; −0.13; +0.03; −0.06; −0.13; −0.03; −0.19; +0.08; where C(2″) is taken as the point of attachment.

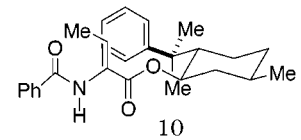
To examine this "exo-extended" working model for acyclic conformational control in such amino ester-derived dienolates, a series of substituted cyclohexanol chiral auxiliaries was installed as indicated in Scheme 5.

(27) The "endo/exo" descriptors refer to dianion position with respect to the cyclohexyl ring. "Endo" here designates conformers possessing approximately a 0° dihedral angle with respect to rotation about the $C^1-O-C^{1'}$–cy bond, where cy refers to the bisector of the $C^{6'}-C^{1'}-C^{2'}$ angle. In the "exo" conformers, the corresponding dihedral angle is 180°. Similarly, "folded" and "extended" conformers are characterized by dihedral angles of approximately 0° and 180°, respectively, about the $C^2-{}^1C-C^{1'}$ bond.

(28) Of course, by the Curtin−Hammett principle, if under the reaction conditions, the interconversion of conformers **I** and **II**, say, were fast relative to their transformation to products, the product distribution would be governed by the relative energies of the transition states leading to the products, rather than by the relative energies of **I** and **II**. In such a situation, conformational prefererences in the transition states need not directly reflect ground state conformational preferences.

(29) In exo-extended conformer **I**, here, the p-orbitals of the opposing π-surfaces are offset, rather than directly overlaid.[22] Thus the atom-to-atom distances we obtain using the MacSpartan Plus program slightly overestimate the distance between the two π-surfaces.

Table 1. Chiral Vinylglycine-Derived Dianion Dienolates: Diastereoselectivity as a Function of Auxiliary

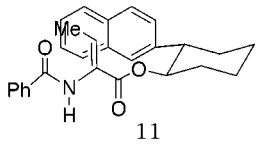


10

(**A**) LDA, 2 n-BuLi
HMPA-THF -78° C

BnBr
Isobutyl Iodide

α:γ ratio	Diast. ratio	Yield	Product
1:1	7:1	62 %	13
only α	32:1	64 %	14

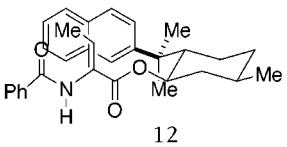


11

(**A**)

BnBr
Isobutyl Iodide

3:2	2:1	50 %	15
only α	14:1	(52 %)[a]	16



12

(**A**)

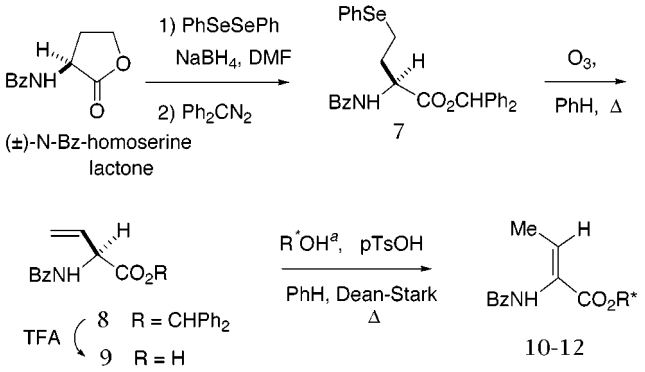
BnBr
Isobutyl Iodide

1:1	10:1	70 %	17
only α	≥ 98:2	81 %	18

[a] Yield based on recovered starting material.

Our vinylglycine synthesis[12c] was modified to provide access to the corresponding benzamido acid. The auxiliary could then be installed by direct incubation of this acid with the auxiliary, under catalysis by *p*-TsOH. Note that isomerization from the vinylglycine to the conjugated dehydrobutyrine system occurs under these conditions.

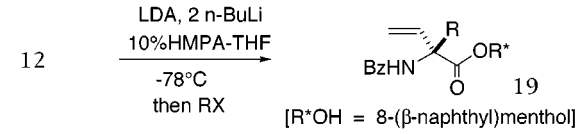
Scheme 5. Toward Chiral, Vinylglycine-Derived Enolates: Installation of the Chiral Auxiliaries[a]

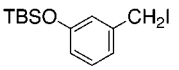
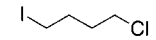
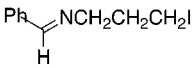
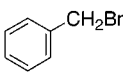
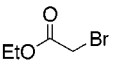


[a] R*OH = *trans*-2-naphthylcyclohexanol, (−)-8-phenylmenthol, or (−)-8-(*β*-naphthyl)menthol.

Next, three aryl-cyclohexyl-type auxiliaries were evaluated for diastereoselectivity and regioselectivity (α- vs *γ*-reactivity) in alkylation reactions of their derivative dianion dienolates (see Table 1). Benzyl bromide and isobutyl iodide were initially screened as electrophiles. Regioselectivity was found to be electrophile-dependent, with the harder electrophiles (e.g., isobutyl iodide) showing the greatest preference for deconjugative (α) alkylation. Note that softer electrophiles here are deemed to be those in which a *π*-system is adjacent to the C−X bond. For these systems, *π*−*σ** overlap might be expected. The *trans*-2-(*β*-naphthyl)cyclohexanol auxiliary,[20c] in which the aromatic blocking group is attached directly to the ring, proved less effective than the 8-arylmenthol-type auxiliaries at controlling the facial approach of the alkyl halide. While the Corey auxiliary[(−)-8-phenylmenthol][19] showed good diastereoselectivity and yield, the d'Angelo auxiliary [(−)-8-(*β*-naphthyl)menthol][20a] was clearly superior in this system (BnBr, 70%, 10:1 dr; i-BuI, 81%, ≥98:2 dr).

Table 2



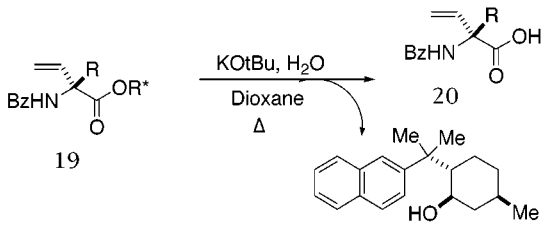
RX	α-vinyl AA (No.)	α:γ ratio	Diast. ratio[a]	Yield[b]
	m-Tyr (19a)	2:1	94:6	65%
$(CH_3)_2CHCH_2I$	Leu (18)	α	≥ 98:2	81%
CH_3CH_2I	butyrine (19c)	α	≥ 98:2	64%
	Lys (19d)	α	95:5	72%
	Orn (19e)	10:1	97:3	74%
	Phe (17)	1:1	91:9	70%
	Asp[c] (19g)	2:1	≥ 98:2	70%
$(CH_3)_2CHI$	Val (19h)	α	≥ 98:2	66%
$CH_3CH_2CH_2I$	norVal (19i)	3:1	≥ 98:2	71%
$BrCH_2C{\equiv}CTMS$	propargyl-Gly (19j)	4:1	≥ 98:2	70%

[a] Diastereomeric ratios based on ^{1}H NMR (500 MHz). The vinylic protons are resolved in the spectrum of the diastereomers. [b] Yields given are total alkylation yields and reflect the sum of α- and *γ* -alkylation products, which in most cases were inseparable by flash chromatography. [c] In this case, the α- and *γ*-alkylation products could be separated by flash chromatography.

Given the promising results obtained with the d'Angelo auxiliary, its vinylglycine-derived dianionic dienolate was further investigated. In fact, as can be seen in Table 3, a considerable variety of important amino acid side chains can directly be introduced, including those of *m*-tyrosine

and ornithine, for which the corresponding α-vinyl AAs (as the racemates) are known AADC suicide substrates.[1] Highest yields are obtained in the presence of HMPA as cosolvent, suggesting that the reactive form of the dienolate is monomeric. Under such conditions, yields are consistently in the 65−80% range and diastereoselectivities are very good to excellent (82% to ≥96% de). Consistent with the initial screening results, α/γ ratios are most favorable for hard electrophiles. The fact that secondary alkyl halides (e.g., isopropyl iodide) also react well with this sterically demanding dienolate is also worthy of note.

Table 3. Efficient Auxiliary Release under Elevated Temperature Gassman Conditions



entry	R	α-benzoamido acid (%)	recovered auxiliary (%)
a	*m*-(HO)$C_6H_4CH_2$−	53	94
b	$(CH_3)_2CHCH_2$−	73	92
c	CH_3CH_2−	62	90
d	$H_2NCH_2CH_2CH_2CH_2$−[a]	78	87
e	$H_2NCH_2CH_2CH_2$−[b]	69	94
f	$PhCH_2$−	76	90
g	HO_2CCH_2−[c]	72	87
h	$(CH_3)_2CH$−	76	80
i	$CH_3CH_2CH_2$−	78	72

[a] Compound **25d** is actually employed here. [b] Hydroxide concentration was increased (10 equiv of H_2O, 10 equiv of KOtBu) to prevent formation of the lactam. [c] The ethyl ester in the side chain was also cleaved under the reaction conditions to yield the diacid.

These alkylation products may be de-esterified with recovery of the chiral auxiliary using a modified Gassman "anhydrous hydroxide" procedure,[30] in which dioxane is substituted for diethyl ether, enabling the reaction to be run at a higher temperature. At refluxing Et_2O temperatures, these hindered esters are essentially inert to cleavage. By contrast, upon heating at a reflux with 2−3 equiv of H_2O and 8−10 equiv of KOtBu in dioxane for about 8 h, one recovers the chiral auxiliary and isolates the α-benzamido acid in high yield and purity (Table 3). The two are separated by simple extraction. It is worthy of note that in cases where **19** contains some γ-alkylation product, this α,β-unsaturated ester apparently decomposes under these basic reaction conditions, essentially providing for purification of the desired α-alkylated isomer in situ. This simple modification of the Gassman ester cleavage protocol is likely to find application elsewhere for sterically encumbered systems. In an interesting twist, exposure of the ornithine derivative to these conditions, results in a mixture of δ-lactam and δ-amino acid. If desired, one can channel all material to the δ-amino acid (albeit in slightly lower yield) by increasing both the amount of H_2O and the reaction time (see entry e and the Experimental Section).

Final deprotection of the benzamido acids is accomplished using 6 N HCl to obtain enantiomerically enriched α-vinyl amino acids (Table 4). In the two cases where literature values were available, our optical rotations were consistent with those previously reported by Seebach's group [for L-α-vinylbutyrine: $[\alpha]_D$ + 30.2 (*c* 1 H_2O); $[\alpha]^{13a}$ +27.7 (*c* 1 H_2O); for L-α-vinylphenyalanine: $[\alpha]_D$ (82% ee) +13.1 (*c* 1 CH_3OH); $[\alpha]^{13b}$ −16.6 (*c* 1 CH_3OH) for D-α-vinylphenylalanine].

Table 4. Hydrolysis to the Free L-α-Vinyl Amino Acids

entry	R	yield (%)	er (%)	$[\alpha]_D$
a	*m*-(HO)$C_6H_4CH_2$−	88[a]	94:6	+7.85
b	$(CH_3)_2CHCH_2$−	96	≥98:2	+37.5
c	CH_3CH_2−	63	≥98:2	+30.2[b]
d	$H_2NCH_2CH_2CH_2CH_2$−	87	96.5:3.5	+12.6
e	$H_2NCH_2CH_2CH_2$−	96	97:3	+18.8
f	$PhCH_2$−	85	91:9	+13.1[c]
g	HO_2CCH_2−	98[a]	≥98:2	+26.3
h	$(CH_3)_2CH$−	98	≥98:2	+30.7

[a] Isolated as the hydrochloride salt. [b] $[\alpha]^{13a}$ = +27.7 L-α-vinylbutyrine. [c] $[\alpha]^{13b}$ = −16.6 D-α-vinylphenylalanine.

Finally, motivated by our recent observation that (±)-vinyllysine inhibits lysine decarboxylase,[1] we sought to apply this methodology to an asymmetric synthesis of L-α-vinyllysine. This could be achieved starting from the alkylation product obtained with 1-chloro-4-iodobutane (**19d**) (Table 2). ϵ-Halogen exchange is first performed with NaI, providing iodide **22d**, which is then displaced by azide ion. Reduction of the azide is then accomplished with PPh_3. Hydrolysis of the resulting phosphine imine yields the free amine.[31] Ester deprotection of **25d** using the modified Gassman procedure[30] is followed by benzamide hydrolysis (see Tables 3 and 4) to give enantiomerically enriched L-α-vinyllysine (Scheme 6).

Conclusions

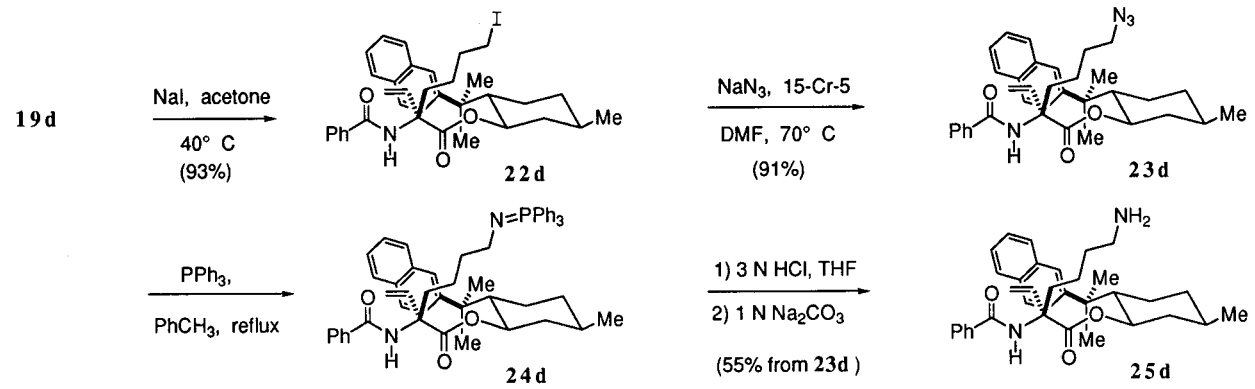
In summary, we describe herein a strategy for engineering effective, acyclic stereocontrol elements into dianionic dienolates derived from vinylglycine and 8-arylmenthyl-type auxiliaries. Enolate geometry is envisioned to be chelation-controlled through a favorable syn arrangement of the amidate nitrogen and the enolate oxyanion, both ligated to lithium. Facial selectivity is postulated to be controlled by a favorable soft−soft interaction between the aryl blocking group of the auxiliary and the extended π-system of the dianianic dienolate. Interestingly, semiempirical (PM3) geometry optimizations and calculated heats of formation, also identify the model "exo-extended" conformer of the (d'Angelo auxiliary-derived) dienolate as a particularly favorable conformer.

Consistent with the model, a high degree of acyclic stereocontrol (91:9 to ≥98:2 dr) is achieved in the alkylation of this dienolate with electrophiles representing a range of natural and unnatural amino acid side chains. Following alkylation, the chiral auxiliary may be recovered in excellent yield using a modified Gassman "anhydrous hydroxide" procedure that may prove to be a generally useful method for the cleavage of hindered

(30) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918−920.

(31) For a related Lys side chain elaboration, see: Danzin, C.; Casara, P.; Claverie, N.; Metcalf, B. W. *J. Med. Chem.* **1981**, *24*, 16−20.

Scheme 6. Elaboration of the L-Vinyllysine Side Chain



esters. To our knowledge, this work reports the first asymmetric syntheses of a number of biologically relevant, higher α-vinyl amino acids, including L-α-vinyl-m-tyrosine, L-α-vinylaspartate, L-α-vinylornithine, and L-α-vinyllysine. Furthermore, given that the pseudoenantiomer of the d'Angelo auxiliary is now available via a chemoenzymatic route developed by Comins and Salvador,[32] this approach should also be amenable to the synthesis of D-α-vinyl amino acids.

Experimental Section

General Methods. All reactions were conducted under an argon atmosphere using flame-dried glassware unless otherwise noted. Diisopropylamine, MeCN, and CH_2Cl_2 were distilled from CaH_2. Benzene, toluene, THF, and Et_2O were distilled from sodium benzophenone ketyl. HMPA was distilled, in vacuo, from Na. *n*-Butyllithium in hexanes (nominally 1.6 M) was purchased from Aldrich and titrated[33] before each use. Elemental analyses were carried out by M−H−W Labs (Phoenix, AZ). For chiral dianion alkylations, diastereomeric product ratios (dr's) were determined by integration of the ^{1}H NMR (500 MHz) spectra. The peaks used to assess dr are indicated in each individual experimental write-up. Where only one diastereomer is observed, we report ≥98:2 dr = ≥96% de, assuming a 2% detection limit.

General Procedure A. (1′*R*,2′*S*,5′*R*)-8′-Phenylmenthyl *N*-Benzoyl-(Z)-dehydrobutyrinate (10). To a solution of **9** (483 mg, 2.36 mmol) in benzene (18 mL) was added (1*R*,2*S*,5*R*)-8-phenylmenthol[19] (476 mg, 2.05 mmol) and *p*-TsOH (156 mg, 0.82 mmol). The solution was heated at a reflux using a Dean−Stark trap for 2−3 d. After cooling, $NaHCO_3$ (aqueous, 25 mL) was added, and the solution was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (EtOAc 10% /hexane) afforded **10** (442 mg, 51%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, J = 6.4 Hz, 3 H), 0.88−0.99 (m, 2 H), 1.18 (s, 3 H), 1.30 (s, 3 H), 1.47−1.50 (m, 1 H), 1.66 (d, J = 7.25 Hz, 3 H), 1.68−1.70 (m, 2 H), 1.82−1.87 (m, 2 H), 2.09−2.14 (dt, J = 3.6, 10.4 Hz, 1 H), 4.90−4.96 (dt, J = 4.4, 10.8 Hz, 1 H), 6.16 (quart, J = 7.25 Hz, 1 H), 6.85 (s, 1 H), 7.12 (t, J = 7.25 Hz, 1 H), 7.21−7.29 (m, 4 H), 7.46 (t, J = 7.2 Hz, 2 H) 7.53 (t, 7.2 Hz, 1 H), 7.77 (app d, 7.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 21.7, 23.3, 26.3, 29.3, 31.2, 34.3, 34.4, 39.4, 41.5, 50.5, 75.3, 124.7, 125.9, 127.3, 128.0, 128.5, 131.7, 133.7, 134.2, 152.1, 163.5, 165.1; IR (ATR) 3285−3373, 1714, 1665 cm^{-1}. Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.97; N, 3.33. Found: C, 76.85; H, 7.65; N, 3.30. The *Z*-alkene geometry was assumed by analogy with **12** (vide infra).

(±)-*trans*-2-(*β*-Naphthyl)cyclohexyl *N*-Benzoyl-(Z)-dehydrobutyrinate (11). From (±)-*trans*-2-(*β*-naphthyl)-cyclohexanol[20c] (453 mg, 2.21 mmol) following general procedure A, **11** was obtained [(400 mg, 50% (53% based on recovered SM)], after flash chromatography (10% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36−1.59 (m, 3 H), 1.63−1.71 (m, 1 H), 1.65 (d, J = 7.39 Hz, 3 H), 1.79−1.95 (m, 2 H), 1.97−2.02 (m, 1 H), 2.23−2.30 (m, 1 H), 2.86−2.95 (dt, J = 3.8, 12.1 Hz, 1 H), 5.06−5.13 (dt, J = 4, 11 Hz, 1 H), 6.60 (quart, J = 7.15 Hz, 1 H), 7.17 (s, 1 H), 7.31−7.52 (m, 6 H), 7.62 (s, 1 H), 7.69−7.80 (m, 3 H), 7.74 (d, J = 8 Hz, 2 H); ^{13}C NMR (125 MHz) δ 14.6, 24.5, 25.6, 32.0, 33.6, 49.6, 77.5, 125.2, 125.6, 125.7, 125.8, 126.0, 127.1, 127.4, 127.8, 128.2, 128.3, 131.6, 132.3, 132.4, 133.4, 133.8, 140.4, 163.7, 164.9; IR (ATR) 3325−3364, 1716, 1662 cm^{-1}. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.38. Found: C, 77.99, H, 6.72; N, 3.15. The *Z*-alkene geometry was assumed by analogy with **12** (vide infra).

(1′*R*,2′*S*,5′*R*)-8′-(*β*−Naphthyl)menthyl *N*-Benzoyl-(Z)-dehydrobutyrinate (12). From (1′*R*,2′*S*,5′*R*)-8′-(*β*-naphthyl)-menthol[20a] (3.20 g, 11.3 mmol) following general procedure A, **12** was obtained (3.40 g, 64%, after flash chromatography (10% EtOAc/ hexane): $[\alpha]_D$ −34.9° (*c* 1.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6 Hz, 3 H), 0.88−1.08 (m, 2 H), 1.12 (d, J = 7 Hz, 3 H), 1.18−1.32 (m, 1 H), 1.25 (s, 3 H), 1.37−1.53 (m, 1 H), 1.42 (s, 3 H), 1.65−1.83 (m, 2 H), 1.94−1.99 (m, 1 H), 2.18−2.27 (dt, J = 3, 12 Hz, 1 H), 4.98 (dt, J = 4, 11 Hz, 1 H), 5.90 (q, J = 7 Hz, 1 H), 6.34 (s, 1 H), 7.35−7.47 (m, 4 H), 7.49−7.54 (m, 2 H), 7.58−7.60 (m, 3 H), 7.70−7.76 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 21.7, 22.2, 26.3, 30.0, 31.3, 34.5, 39.5, 41.6, 50.1, 74.9, 122.7, 125.1, 125.3, 125.5, 127.2, 127.3, 127.8, 128.4, 131.2, 131.6, 133.4, 134.1, 134.2, 149.7, 163.4, 165.0. IR (ATR) 3220−3400, 1717, 1700, 1696, 1653 cm^{-1}. Anal. Calcd for $C_{31}H_{35}NO_3$: C, 79.29; H, 7.51; N, 2.98. Found: C, 78.43; H, 7.86; N, 2.89.Long-range carbon−hydrogen decoupling experiments were employed to find the three-bond C−H coupling constant between the ester carbonyl carbon and the vinylic methine proton. The value obtained (3.8 Hz) points to the *Z*- alkene geometry in **12**.[34] [The fully proton-coupled ester carbonyl exhibited a triplet ($J_{1,3}$ = 3−4 Hz). Decoupling the vinylic proton, produced a doublet ($J_{1,3}$ = 3.1 Hz) for this carbon. Similarly, decoupling the 1′-cyclohexyl proton, also led to a doublet ($J_{1,3}$ = 3.8 Hz)].

General Procedure B. (1′*R*,2′*S*,5′*R*)-8′-Phenylmenthyl *N*-Benzoyl-L-α-vinylphenylalaninate (13). To a solution of diisopropylamine (24 μL, 0.18 mmol) and HMPA (1 mL) in THF at −78 °C was added *n*-butyllithium (0.15 mL, 1.3 M in *n*-hexane). The resulting solution was stirred for 20 min at 0 °C and then cooled to −78 °C. Then **10** (70 mg, 0.17 mmol) in THF (4 mL) at −78 °C was added via cannula, followed by butyllithium (0.26 mL, 1.3 M in *n*-hexane). The resulting deep-

(32) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656−4661.

(33) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87−88.

(34) Marshall, J. L. *Carbon−Carbon and Carbon-Proton NMR Couplings: Applications to Organic Stereochemistry and Conformational Analysis* (Verlag Chemie International, 1983) pp 35−38.

red solution was stirred for 5 min at −78 °C. Benzyl bromide (44 μL, 0.37 mmol) in THF (0.4 mL) at −78 °C was then added via cannula. After TLC indicated completion of the reaction [45 min in this case; eluent: 20% EtOAc/hexanes; R_f(**10**) = 0.5; R_f(**13**) = 0.7], the reaction mixture was poured into Et_2O (20 mL) and NH_4Cl (aq, 20 mL). After further extraction of the reaction mixture with Et_2O (3 × 10 mL), the combined organics were dried ($MgSO_4$), filtered, and evaporated. Flash chromatography on silica gel (10% EtOAc/hexane) provided **13** and its γ-alkylation isomer in a 1:1 ratio (53.1 mg, 62% overall yield, 74% de for **13**). In this case, the vinylic methine protons were resolved and could be integrated to obtain the dr. For **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87−0.99 (d, J = 6.4 Hz, 3 H), 0.94−1.07 (m, 2 H), 1.19 (s, 3 H), 1.30 (s, 3 H), 1.66−1.68 (m, 1 H), 1.77−1.80 (m, 1 H), 1.99−2.02 (m, 1 H), 2.05−2.11 (m, 1 H), 2.38−2.46 (m, 1 H), 2.74−2.70 (m, 1 H), 3.32 (d, J = 13.7 Hz, 1 H), 3.69 (d, J = 13.7 Hz, 1 H), 4.91−4.96 (dt, J = 4, 10.4 Hz, 1 H), 5.37 (d, J = 17.3 Hz, 1 H), 5.30 (d, J = 10.4 Hz, 1 H), 5.89−5.95 (dd, J = 10.4, 17.3 Hz, 1 H), 6.88 (s, 1 H), 7.11−7.21 (m, 4 H), 7.26−7.28 (m, 5 H), 7.45−7.48 (m, 2 H), 7.52−7.53 (m, 2 H), 7.72 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 24.2, 26.5, 27.3, 28.6, 31.4, 34.4, 39.3, 41.6, 50.0, 65.5, 78.5, 124.9, 125.4, 125.5, 126.9, 127.4, 128.0, 128.4, 130.5, 131.4, 131.7, 135.9, 136.6, 137.2, 152.0, 163.4, 170.7. Anal. Calcd for $C_{34}H_{39}NO_3$: C, 80.12; H, 7.71; N, 2.75. Found (with α/γ mixture): C, 79.78; H, 7.93; N, 2.60.

(1′*R*,2′*S*,5′*R*)-8′-Phenylmenthyl *N*-Benzoyl-L-α-vinylleucinate (14). From **10** (40 mg, 0.10 mmol) and isobutyl iodide (24 μL, 0.21 mmol), following general procedure B, was obtained **14** (29 mg, 64%, 94% de), after flash chromatography. In this case, the dr was determined by integration of the vinylic methine protons: $[\alpha]_D$ −1.77 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85−0.91 (m, 9 H), 0.92−1.06 (m, 2 H), 1.21 (s, 3 H), 1.32 (s, 3 H), 1.39−1.47 (m, 2 H), 1.54−1.63 (m, 3 H), 1.80−1.84 (dd, J = 6, 14.1 Hz, 1H), 2.01−2.07 (dt, J = 3.2, 12.0 Hz, 1 H), 2.09−2.12 (m, 1 H), 2.41−2.45 (dd, J = 6, 14.1 Hz, 1 H), 4.83−4.88 (dt, J = 4.0, 10.4 Hz, 1 H), 5.19 (d, J = 10.4 Hz, 1 H), 5.22 (d, J = 17.3 Hz, 1 H), 5.72−5.78 (dd, J = 10.4, 17.3 Hz, 1 H), 7.14 (s, 1 H), 7.13−7.29 (m, 5 H), 7.45 (t, J = 7.25 Hz, 2 H), 7.51 (t, J = 7.25 Hz, 1 H), 7.80 (app d, J = 7.25 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 23.5, 23.8, 24.9, 25.2, 27.3, 29.1, 31.4, 34.4, 20.1, 41.3, 42.8, 49.9, 64.7, 78.4, 115.1, 125.4, 125.7, 126.9, 128.0, 128.5, 131.4, 135.0, 137.1, 150.5, 165.7, 172; IR (ATR) 3390−3400, 1700, 1617, 1559 cm^{-1}. Anal. Calcd for $C_{31}H_{41}NO_3$: C, 78.27; H, 8.68; N, 2.94. Found: C, 77.73; H, 8.22; N, 2.90.

(±)-*trans*-(2-Naphthyl)cyclohexyl *N*-Benzoyl-α-vinylphenylalaninate (15). From **11** (105 mg, 0.25 mmol) and benzyl bromide (76 μL, 0.64 mmol), following general procedure B, was obtained **15** (72.7 mg, 50%, 34% de), as a 3:2 ratio of α- to γ-alkylation products after flash chromatography (10% EtOAc/hexane). In this case, both the vinylic methylene and the benzylic protons were resolved and could be integrated to obtain the dr.

(±)-*trans*-(2-Naphthyl)cyclohexyl *N*-Benzoyl-α-vinylleucinate (16). From **11** (48.5 mg, 0.12 mmol) and isobutyl iodide (29 μL, 0.26 mmol), following general procedure B, was obtained **16** (22.1 mg, 52% based on recovered starting material, 86% de), after flash chromatography. In this case, the dr was obtained by integration of the vinylic methine protons: $[\alpha]_D$ +0.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (d, J = 6.68 Hz, 3 H), 0.70 (d, J = 6.68 Hz, 3 H), 1.34−1.59 (m, 4 H), 1.61−2.05 (m, 5 H), 2.23−2.27 (m, 1 H), 2.35−2.42 (dd, J = 5.7, 14.0 Hz, 1 H), 2.85−2.94 (dt, J = 3.5, 10.9 Hz, 1 H), 4.17 (d, J = 10.2 Hz, 1 H), 4.56 (d, J = 17 Hz, 1 H), 5.12−5.19 (m, 1 H), 5.22−5.30 (dd, J = 10.2, 17 Hz, 1 H), 7.16 (s, 1 H), 7.29−7.35 (m, 1 H), 7.36−7.49 (m, 5 H), 7.58 (app s, 1 H), 7.66 (d, J = 8.3 Hz, 2 H), 7.72−7.78 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 23.4, 24.6, 24.7, 25.6, 32.0, 34.0, 42.0, 50.0, 64.5, 78.5, 113.9, 125.3, 125.4, 125.9, 126.4, 126.7, 127.4, 128.0, 128.2, 128.4, 131.3, 132.4, 133.4, 134.8, 136.3, 139.9, 165.4, 172.4; IR (ATR) 3327−3407, 1700, 1635, 1559 cm^{-1}. Anal. Calcd for $C_{31}H_{35}NO_5$: C, 79.28; H, 7.51; N, 2.98. Found: C, 79.27; H, 7.11; N, 2,88.

(1′*R*,2′*S*,5′*R*)-8′-(β-Naphthyl)menthyl *N*-Benzoyl-L-α-vinylphenylalaninate (17). From **12** (100 mg, 0.21 mmol) and benzyl bromide (55 μL, 0.64 mmol), following general procedure B, was obtained **17** (83.1 mg, 70%, 82% de, the internal vinylic proton for each diastereomer was resolved and could be integrated.), as a 1:1 ratio of α- to γ-alkylation products after flash chromatography (10% EtOAc/hexane). The α-alkylation product, **17** (first eluting) and the γ-alkylation product isomer (second eluting) could be cleanly separated (baseline resolution) by silica gel HPLC (gradient elution: 2% → 9% EtOAc/hexane): ^{1}H NMR (α-alkylation product; 500 MHz, $CDCl_3$) 0.81−0.84 (m, 2H), 0.86 (d, J = 6.4 Hz, 3 H), 1.02−1.09 (m, 2 H), 1.27 (s, 3 H), 1.33 (s, 3 H), 1.42−1.48 (m, 2 H), 2.03−2.05 (m, 1 H), 2.19−2.24 (dt, J = 3.3, 10 Hz, 1 H), 3.20 (d, J = 13.7 Hz, 1 H), 3.35 (d, J = 13.7 Hz, 1 H), 4.90−4.95 (dt, J = 4.1, 10.7 Hz, 1 H), 5.18 (d, J = 17 Hz, 1 H), 5.20 (d, 10.5 Hz, 1 H), 5.74−5.79 (dd, 10.5, 17 Hz, 1 H), 6.73 (bs, 1 H) 6.91−6.93 (m, 2 H), 7.11−7.14 (m, 3 H), 7.38−7.50 (m, 5 H), 7.64−7.66 (m, 3 H), 7.74 (d, J = 8 Hz, 2 H), 7.78−7.79 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 25.5, 27.4, 28.2, 31.4, 34.5, 39.3, 40.2, 41.3, 49.6, 65.2, 78.4, 116.1, 123.3, 124.8, 125.3, 126.0, 126.8, 126.9, 127.4, 127.6, 127.9 (2 C), 128.5, 130.5, 131.5 (2 C), 133.3, 134.9, 135.7, 136.4, 148.4, 166.4, 170.7; IR (ATR) 3200−3400, 1721, 1719, 1679, 1675 cm^{-1}. Anal. Calcd for $C_{38}H_{41}NO_3$: C, 81.53; H, 7.39; N, 2.50. Found: C, 81.78; H, 6.91; N, 2.15.

^{1}H NMR (γ-alkylation product; 500 MHz, $CDCl_3$) 0.87 (d, J = 6.4 Hz, 3 H), 0.89−0.99 (m, 2 H), 1.21−1.24 (m, 2 H), 1.27 (s, 3 H), 1.41 (s, 3 H), 1.50−1.53 (m, 2 H), 1.68−1.71 (m, 1 H), 1.82−1.99 (m, 3 H), 2.18−2.23 (dt, J = 3.4, 13 Hz, 1 H); 2.46−2.49 (m, 2 H); 4.96−5.01 (dt, J = 4.2, 10.6 Hz, 1 H), 6.03 (t, J = 7.2 Hz, 1 H), 6.26 (bs, 1 H), 7.10−7.11 (m, 2 H), 7.16−7.19 (m, 1 H), 7.26−7.27 (m, 2 H), 7.37−7.44 (m, 3 H), 7.48−7.55 (m, 4 H), 7.62 (s, 1 H), 7.71 (d, J = 8 Hz, 2 H), 7.74−7.75 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 23.1, 26.4, 29.3, 30.4, 31.3, 33.9, 34.5, 39.6, 41.5, 50.2, 75.2, 122.9, 124.9, 125.0, 125.3, 125.9, 127.2, 127.3 (2 C), 127.9, 128.3 (2 C), 128.4 (2 C), 131.2, 131.6, 133.4, 135.1, 137.4, 141.3, 149.5, 163.3, 165.6.

(1′*R*,2′*S*,5′*R*)-8′-(β-Naphthyl)menthyl *N*-Benzoyl-L-α-vinylleucinate (18). From **12** (250 mg, 0.53 mmol) and isobutyl iodide (0.12 mL, 1.06 mmol), following general procedure B was obtained **18** (228 mg, 81%, ≥96% de) after flash chromatography (10% EtOAc/hexane): $[\alpha]_D$ +8.10 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, J = 6.5 Hz, 3 H), 0.85 (d, J = 6.5 Hz, 3 H), 0.89 (d, J = 6 Hz, 3 H), 0.97−1.12 (m, 3 H), 1.31 (s, 3 H), 1.42 (s, 3 H), 1.44−1.62 (m, 4 H), 1.67−1.74 (dd, J = 6.4, 14 Hz, 1 H), 2.11−2.32 (m, 2 H), 2.25−2.32 (dd, J = 6.4 Hz, 14 Hz, 1 H), 4.88−4.96 (dt, J = 4, 11 Hz, 1 H), 5.13 (d, J = 10.5 Hz, 1 H), 5.18 (d, J = 17 Hz, 1 H), 5.65−5.75 (dd, J = 10.5, 17 Hz, 1 H), 7.15 (s, 1 H), 7.39−7.57 (m, 6 H), 7.64 (br s, 1 H), 7.70−7.23 (m, 1 H), 7.34−7.80 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 23.4, 23.7, 24.8, 25.2, 27.4, 28.8, 31.4, 34.4, 40.2, 41.3, 42.2, 49.6, 64.5, 78.4, 115.1, 123.4, 124.8, 125.3, 125.9, 126.9, 127.3, 127.6, 127.9, 128.6, 131.4, 131.5, 133.3, 134.9, 136.9, 148.2, 165.7, 172.5; IR (ATR) 3300−3400, 1733, 1675, 1653 cm^{-1}; MS (FAB,3-NBA) 526 (7, MH^+), 355 (30), 281 (47), 146 (100). Anal. Calcd for $C_{35}H_{43}NO_3$: C, 79.96; H, 8.24; N, 2.66. Found: C, 79.82; H, 8.20; N, 2.58.

3′-(*tert*-Butyldimethylsilyoxy)benzyl Iodide (26). To 3′-(*tert*-butyldimethylsilyloxy) benzyl bromide (247 mg, 0.82 mmol) were added acetone (2 mL) and NaI (predried in vacuo at 210 °C) (369 mg, 2.46 mmol), and this solution was stirred in the dark for 96 h. The acetone was then evaporated, and the residue was taken up in Et_2O (20 mL) and extracted with $Na_2S_2O_4$ (3 × 15 mL), dried ($MgSO_4$), and evaporated to give **26** (238 mg). The iodide was used directly in the next step, without further purification. However, if desired, an analytical sample could be obtained by SiO_2 chromatography (hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 6 H), 0.97 (s, 9 H), 4.37 (s, 2 H), 6.68−6.73 (m, 1 H), 6.83−6.85 (m, 1 H), 6.93−6.96 (m, 1 H), 7.09−7.16 (dt, J = 3.5 Hz, 8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.44, 5.51, 18.1, 26.6, 119.6, 120.5, 121.6, 129.6, 140.5, 155.7; IR (ATR) 2929, 1276, 1169 cm^{-1}; MS (FAB 3-NBA) 221 (87 M−I), 147 (100); HRMS (FAB 3-NBA) calcd for $C_{13}H_{21}OSiI$ (M − I) 221.1361, obsd 221.0857.

(1″*R*,2″*S*,5″*R*)-8″-(*β*-Naphthyl)menthyl *N*-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-L-α-vinyl-*m*-tyrosinate (19a). From **12** (200 mg, 0.43 mmol) and 3′(*tert*-butyldimethylsilyloxy)-benzyl iodide **26** (32.9 mg, 0.94 mmol) following general procedure B, was obtained **19a** (189.1 mg, 65%, 88% de, based upon integration of the vinylic methine protons) as a 2:1 ratio of α to γ after flash chromatography (10% EtOAc/hexane): ^{1}H NMR (α-product, 500 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 0.80−0.88 (m, 5 H), 0.90 (s, 9 H), 0.91−1.06 (m, 2 H), 1.33 (s, 3 H), 1.41 (s, 3 H), 1.50−1.56 (m, 1 H), 2.02−2.05 (m, 1 H), 2.16−2.23 (dt, *J* = 1.3, 8.0 Hz, 1 H), 2.41 (t, *J* = 7.4 Hz, 1 H), 3.15 (d, *J* = 13.7 Hz, 1 H), 3.37 (d, *J* = 13.7, 1 H), 4.89−4.95 (dt, *J* = 3.3, 7.4 Hz, 1 H), 5.18 (d, *J* = 17.4 Hz, 1 H), 5.22 (d, *J* = 11.1 Hz, 1 H), 5.75−5.81 (dd, *J* = 11.1, 17.4 Hz, 1 H), 6.52−6.71 (m, 3 H), 6.79 (s, 1 H), 6.98−7.01 (t, *J* = 7.6 Hz, 1 H), 7.38−7.59 (m, 6 H), 7.62−7.66 (m, 1 H), 7.69−7.81 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, 21.6, 25.6, 27.4, 28.4, 31.4, 33.8, 34.5, 39.4, 41.2, 41.6, 45.4, 49.7, 65.1, 78.4, 116.0, 118.5, 122.3, 123.2, 123.4, 123.5, 124.8, 125.0, 125.3, 125.9, 126.9, 127.2, 127.3, 127.9, 128.4, 128.5, 131.4, 131.5, 133.3, 134.8, 136.5, 148.4, 166.1, 170.8; IR (ATR) 3300−3400, 1684, 1652 cm^{-1}. Anal. Calcd for $C_{44}H_{55}NO_4Si$: C, 76.59; H, 8.03; N, 2.02. Found: C, 76.29; H, 8.20; N, 1.93.

(1′*R*,2′*S*,5′*R*)-8′-(*β*-Naphthyl)menthyl *N*-Benzoyl-L-α-vinylbutyrinate (19c). From **12** (100 mg, 0.21 mmol) and ethyl iodide (25 μL, 0.30 mmol), following general procedure B, was obtained **19c** (69.9 mg, 66%, ≥96% de), as a 12:1 ratio of α- to γ-alkylation products after flash chromatography (10% EtOAc/hexane): $[\alpha]_D$ +4.08 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (t, *J* = 7 Hz, 3 H), 0.77−0.86 (m, 1 H), 0.88 (d, *J* = 6 Hz, 3 H), 0.97−1.10 (m, 2 H), 1.33 (s, 3 H), 1.41 (s, 3 H), 1.42−1.58 (m, 3 H), 1.86−1.93 (m, 1 H), 2.04−2.15 (m, 2 H), 2.41−2.48 (m, 1 H), 4.91−5.00 (dt, *J* = 4, 10.5 Hz, 1 H), 5.11 (d, *J* = 10.5 Hz, 1 H), 5.20 (d, *J* = 17 Hz, 1 H), 5.68−5.77 (dd, *J* = 10.5, 17 Hz, 1 H), 7.03 (s, 1 H), 7.39−7.57 (m, 7 H), 7.63−7.66 (m, 1 H), 7.67−7.74 (m, 1 H), 7.75−7.82 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 21.7, 25.2, 27.3, 27.5, 29.0, 31.4, 34.4, 40.3, 41.4, 49.6, 66.4, 77.9, 115.5, 123.4, 124.8, 125.3, 125.9, 126.9, 127.2, 127.3, 127.5, 127.9, 128.5, 131.5, 133.3, 134.8, 135.8, 148.1, 165.6, 172.1; IR (ATR) 3220−3400, 1717, 1674, 1669 cm^{-1}. Anal. Calcd for $C_{33}H_{39}NO_3$: C, 79.64; H, 7.89; N, 2.81. Found: C, 79.24; H, 7.60, N, 2.82.

(1″*R*,2″*S*,5″*R*)-8″-(*β*-Naphthyl)menthyl *N*-Benzoyl-L-α-(4′-chloro)butyl-α-vinylglycinate (19d). From **12** (200 mg, 0.43 mmol) and 1-chloro-4-iodobutane (0.16 mL, 1.27 mmol) following general procedure B was obtained **19d** (170 mg, 72%, 90% de, as judged from the vinylic methine integrals), after flash chromatography (10% EtOAc/hexane): $[\alpha]_D$ +8.55 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82−0.86 (m, 1 H), 0.88 (d, *J* = 6 Hz, 3 H), 1.04−1.13 (m, 2 H), 1.22−1.33 (m, 3 H), 1.31 (s, 3 H), 1.40 (s, 3 H), 1.42−1.58 (m, 2 H), 1.66−1.74 (m, 2 H), 1.79−1.85 (dt, *J* = 4.8, 13 Hz, 1 H), 2 0.07−2.10 (m, 1 H), 2.15−2.21 (dt, *J* = 3.6, 12.4 Hz, 1 H), 2.39−2.44 (dt, *J* = 4, 12.8 Hz, 1 H), 3.40−3.45 (m, 1 H), 3.48−3.53 (m, 1 H), 4.93−4.98 (dt, *J* = 4, 10.4 Hz, 1 H), 5.09 (d, *J* = 10.4 Hz, 1 H), 5.19 (d, *J* = 17 Hz, 1 H), 5.58−5.64 (dd, *J* = 10.4, 17 Hz, 1 H), 7.13 (s, 1 H), 7.40−7.53 (m, 7 H), 7.63−7.64 (m, 1 H), 7.72−7.79 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.7, 25.6, 27.4, 28.5, 31.4, 32.2, 33.2, 34.3, 40.2, 41.4, 44.8, 49.5, 64.8, 78.2, 115.7, 123.4, 124.8, 125.3, 125.9, 126.9, 127.0, 127.3, 127.5, 127.8, 128.6, 131.6, 133.3, 134.3, 135.7, 148.1, 165.7, 171.9; IR (ATR) 3310−3418, 1717, 1653 cm^{-1}. Anal. Calcd for $C_{35}H_{42}NO_3Cl$: C, 75.04; H, 7.55; N, 2.50. Found: C, 74.91; H, 7.25; N, 2.35.

(1*R*,2′*S*,5′*R*)-8′-(*β* -Naphthyl)menthyl *N*-Benzoyl-L-α-vinylornithinate (19e). From **12** (200 mg, 0.43 mmol) and 1-benzaldimino-3-iodopropane[31] (255 mg, 0.94 mmol), general procedure B was followed as before. However, in this case the crude product mixture was taken up in THF (4 mL) and 3 N HCl (4 mL) and was allowed to stir at 25 °C for 14 h (to remove the benzylidene side chain protecting group). A solution of 1 N Na_2CO_3(15 mL) was then added, and the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organics were dried ($MgSO_4$), filtered, and evaporated. Chromatography was then carried out initially with 20% EtOAc/Hex to remove benzaldehyde and then with 5%MeOH/ CH_2Cl_2 [1% NH_4OH (sat′d aq)]to elute **19e** (164 mg, 74%, 94% de, as judged from the vinylic methine integrals): $[\alpha]_D$ +2.49 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80−0.90 (m, 2 H), 0.88 (d, *J* = 6.4 Hz,3 H), 1.22−1.40 (m, 2H), 1.32 (s, 3 H), 1.42 (s, 3 H), 1.32−1.55 (m, 2 H), 1.77−1.82 (m, 1 H), 2.05−2.08 (m, 1 H), 2.14−2.28 (m, 6H), 2.59−2.66 (m, 2 H), 4.92−4.97 (dt, *J* = 4, 10.4 Hz, 1 H), 5.09 (d, *J* = 10.8 Hz, 1 H), 5.17 (d, *J* = 17.3 Hz, 1 H), 5.73−5.79 (dd, *J* = 10.8, 17.3 Hz, 1 H), 7.39−7.45 (m, 5 H), 7.47−7.51 (m, 2 H), 7.56 (s, 1 H), 7.64(s, 1 H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 6 Hz, 1 H), 7.79 (app d, *J* = 8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 25.6, 26.8, 27.3, 28.4, 31.3, 31.9, 34.4, 20.2,41.3, 41.3, 49.5, 64.4, 77.8, 115.3, 123.4, 124.8, 125.2, 125.8, 127.0, 127.2, 127.5,127.9, 128.4, 131.4, 131.5, 133.3, 134.7, 135.8, 148.3, 165.9, 171.8; IR (ATR) 3300, 3400, 1725, 1665, 1599 cm^{-1}. Anal. Calcd for $C_{34}H_{42}N_2O_3$: C, 77.53; H, 8.03; N, 5.31. Found: C, 77.13; H, 8.33; N, 5.17.

α-(1′*R*,2′*S*,5′*R*)-8-(*β*-Naphthyl)menthyl *β*-Ethyl *N*-Benzoyl-L-α-vinylaspartate (19 g). From **12** (200 mg, 0.43 mmol) and ethyl bromoacetate (100 μL, 852 μmol) following general procedure B was obtained **19g** (110 mg, ≥96% de) and the corresponding γ-alkyation product **27** (54.6 mg) for a 70% total yield (2:1 ratio of of α- to γ-alkylation products) after flash chromatography (10% EtOAc, hexane). For **19g**: $[\alpha]_D$ −4.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79−0.84 (m, 1 H), 0.87 (d, *J* = 6 Hz, 3 H),0.90−0.97 (q, *J* = 12 Hz, 1 H), 1.03−1.06 (m, 1 H), 1.17−1.20 (t, *J* = 7 Hz, 3 H), 1.32(s, 3 H), 1.42 (s, 3 H), 1.44−1.58 (m, 3 H), 2.13−2.19 (m, 2 H), 2.82 (d, *J* = 17 Hz, 1H), 3.52 (d, *J* = 17 Hz, 1 H), 3.99−4.09 (m, 2 H), 4.95−5.00 (dt, *J* = 4, 10.5 Hz, 1 H),5.12−5.15 (dd, *J* = 1, 10.5 Hz, 1 H), 5.23−5.26 (dd, *J* = 1, 17 Hz, 1 H), 5.54−5.60 (dd, *J* = 10.5, 17 Hz, 1 H), 7.40−7.45 (m, 4 H), 7.47−7.50 (m, 2 H), 7.58 (br s, 1 H), 7.65 (br s, 1 H), 7.76−7.79 (m, 3 H), 7.78 (app d, *J* = 8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 21.7, 25.5, 27.4, 28.6, 31.3, 34.5, 38.3, 40.3, 41.0, 49.6, 60.6, 62.0, 78.4, 116.7,-123.5, 124.8, 125.4, 125.9, 127.0, 127.3, 127.6, 127.9, 128.5, 131.5, 131.6, 133.4, 134.0, 134.6, 148.2, 165.8, 170.2, 170.6; IR (ATR) 3310−3400, 1733, 1670, 1653 cm$^{-1;}$ MS (FAB 3-NBA) 556 (5 MH^+) 281 (42) 147 (100); HRMS (FAB 3-NBA) calcd for $C_{35}H_{41}NO_5$ (MH^+) 556.3063, obsd 556.3059.

α-(1′*R*,2′*S*,5′*R*)-8′-(*β*-Naphthyl)menthyl *δ*-Ethyl *N*-Benzoyldehydrohomoglutamate (27): $[\alpha]_D$ +0.8 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6 Hz, 3 H), 0.89−1.02 (m, 2 H), 1.17−1.21 (m, 1 H), 1.24 (t, *J* = 7.5 Hz, 3 H), 1.26 (s, 3 H), 1.42 (s, 3 H), 1.46−1.52 (m, 1 H), 1.68−1.70 (m, 1 H), 1.76−1.82 (m, 1 H), 1.86−1.91 (m, 2 H), 1.93−1.97 (m, 1 H), 2.05−2.24 (m, 3 H), 4.09−4.13 (q, *J* = 7 Hz, 2 H), 4.95−5.00 (dt, *J* = 4, 10.5 Hz, 1 H), 5.70 (t, *J* = 7.5 Hz, 1 H), 6.98 (s, 1 H), 7.37−7.42 (m, 2 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.50−7.53 (m, 2 H), 7.64−7.67 (m, 3 H), 7.72 (d, *J* = 5.6 Hz, 1 H), 7.76 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 21.7, 23.3, 23.4, 26.5, 29.2, 31.3, 32.1, 34.6, 39.7, 41.5, 50.2, 60.5, 75.5, 123.0, 125.0, 125.3, 125.9, 126.4, 127.2, 127.3, 127.3, 127.9, 128.4, 131.2, 131.7, 133.5, 134.0, 134.8, 149.6, 163.2, 172.6, 173.0; IR (ATR) 3320−3415, 1731, 1678 cm^{-1}; MS (FAB 3-NBA) 556 (32 MH^+) 221 (50), 147 (100); HRMS (FAB 3-NBA) calcd for $C_{35}H_{41}NO_5$ (MH^+) 556.2985, obsd 556.3061.

(1′*R*,2′*S*,5′*R*)-8′-(*β*-Naphthyl)menthyl *N*-Benzoyl-L-α-vinylvalinate (19h). From **12** (200 mg, 0.43 mmol) and isopropyl iodide (0.11 mL, 1.06 mmol) following general procedure B was obtained **19h** (218 mg, 66%, ≥96% de) after flash chromatography (10% EtOAc/hexane): $[\alpha]_D$ −5.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.56 (d, *J* = 7 Hz, 3 H), 0.81 (d, *J* = 7 Hz, 3 H), 0.84−0.97 (m, 2 H), 0.89 (d, *J* = 6 Hz, 3 H), 1.09−1.12 (m, 1 H), 1.28 (s, 3 H), 1.42−1.51 (m, 1 H), 1.45 (s, 3 H), 1.56−1.61 (m, 3 H), 2.19−2.24 (m, 2 H), 4.83−4.88 (dt, *J* = 4, 10.5 Hz, 1 H), 4.96−5.00 (dd, *J* = 1, 17 Hz, 1 H), 5.09−5.12 (dd, *J* = 1, 10.5 Hz, 1 H), 5.92 (s, 1 H), 6.06−6.12 (dd, *J* = 10.5, 17 Hz, 1 H), 7.41−7.45 (m, 3 H), 7.49 (t, *J* = 22 Hz, 2 H), 7.55−7.59 (m, 2 H), 7.66 (br s, 1 H), 7.70−7.73 (m, 3 H), 7.74−7.76 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 16.4, 17.5, 21.8, 26.6, 27.2, 27.3, 31.4, 33.6, 34.7, 40.0, 41.3, 49.1, 66.9, 77.6, 115.2, 123.1, 124.9, 125.2, 125.8, 127.0, 127.1, 127.2, 127.9, 128.5, 131.3, 131.4, 132.0, 133.4, 135.0, 149.2, 166.0, 177.3; IR (ATR) 3210−3380, 1733, 1675, 1652 cm^{-1}; (FAB

3-NBA) 512 (26, MH^+), 401 (14), 248 (100), 147 (57). Anal.Calcd for $C_{34}H_{41}NO_3$: C, 79.80; H, 8.07; N, 2.73. Found: C, 79.92; H, 8.17; N, 2.61.

(1′*R*,2′*S*,5′*R*)-8′-(*β*-Naphthyl)menthyl *N*-Benzoyl-L-α-vinylnorvalinate (19i). From **12** (200 mg, 0.43 mmol) and 1-iodopropane (91 μL, 0.94 mmol) following general procedure B was obtained **19i** [108 mg, 50%, (58% based on recovered starting material), ≥96% de] after flash chromatography as a 3:1 mixture of α/γ alkylation products: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89−0.92 (m, 4 H), 0.88 (s, 3 H), 0.96−1.08 (m, 2 H), 1.16−1.30 (m, 2 H), 1.32 (s, 3 H), 1.42 (s, 3 H), 1.43−1.58 (m, 3 H), 1.78−1.84 (dt, J = 4.4, 13.3 Hz, 1 H), 2.04−2.07 (m, 1 H), 2.13−2.18 (dt, J = 4, 13 Hz, 1 H), 2.35−2.41 (dt, J = 4, 13 Hz, 1H), 4.93−5.00 (dt, J = 4.4, 10.4 Hz, 1 H), 5.09 (d, J = 10.4, 1 H), 5.19, (d, J = 17.3, 1 H), 5.69−5.75 (dd, J = 10.4, 17.3, 1 H), 7.00 (s, 1 H), 7.40−7.56 (m, 7 H), 7.63 (app s, 1 H), 7.73−7.79 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 17.1, 21.7, 25.2, 27.3, 28.9, 31.3, 34.4, 36.5, 41.3, 49.6, 50.2, 64.9, 77.9, 115.3, 123.4, 124.8, 125.3, 126.9, 127.3, 127.5, 127.9, 128.4, 128.5, 131.4, 131.5, 133.3, 134.9, 136.0, 148.1, 165.6, 172.1; IR (ATR) 3300−3400, 1684, 1652 cm^{-1}. Anal. Calcd for $C_{34}H_{41}NO_3$: C, 79.80; H, 8.076; N, 2.74. Found: C, 79.79; H, 7.82; N, 2.52.

(1″*R*,2″*S*,5″*R*)-8″-(*β*-Naphthyl)menthyl *N*-Benzoyl-L-α-(3′-trimethylsilyl)propargyl-α-vinylglycinate (19j). From **12** (100 mg, 0.21 mmol) and 3-bromo-1(trimethylsilyl)-1-propyne (60.2 μL, 0.15 mmol) following general procedure B was obtained **19j** (76.5 mg, 70%, 94% de, as judged from the vinylic methine integrals) as a 4:1 ratio of α/γ after flash chromatography (10% EtOAc/Hex): ^{1}H NMR (α-alkylation product, 500 MHz, $CDCl_3$) δ 0.42 (s, 9 H), 0.87 (d, J = 6 Hz, 3 H), 1.03−1.14 (m, 1 H), 1.32 (s, 3 H), 1.39 (s, 3 H), 1.41−1.55 (m, 3 H), 2.14−2.20 (m, 2 H), 2.81 (d, J = 17 Hz, 1 H), 3.42 (d, J = 17 Hz, 1 H), 4.9−5.0 (dt, J = 4, 10.4 Hz, 1 H), 5.09 (d, J = 10 Hz, 1 H), 5.24 (d, J = 17 Hz, 1 H), 5.46−5.51 (dd, J = 10.4, 17.7 Hz, 1 H), 7.29 (s, 1 H), 7.41−7.52 (m, 6 H), 7.62 (app s, 1 H), 7.75−7.80 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.061, 21.7, 21.8, 25.3, 26.2, 27.3, 28.8, 31.4, 34.4, 40.2, 41.1, 49.5, 50.2, 63.8, 78.4, 88.1, 101.1, 117.0, 123.4, 125.3, 125.4, 125.9, 127.0, 127.2, 127.3, 127.6, 127.8, 128.5, 131.5, 131.5, 134.0, 148.0, 166.1, 170.5; IR (ATR) 3340−3401, 2178, 1724, 1674 cm^{-1}. Anal. Calcd for $C_{37}H_{43}NO_3Si$: C, 76.90; H, 7.50; N, 2.42. Found: C, 77.06; H, 7.15; N, 2.05.

General Procedure C. *N*-Benzoyl-L-α-vinylbutyrine (20c). KOtBu (320 mg, 2.85 mmol), and H_2O (13.6 μL, 0.76 mmol) were added to a solution of **19c** (165 mg, 0.33 mmol) in (3 mL) of 1,4-dioxane, and the resulting solution was heated to 105 °C for 8 h. After cooling, 10% HCl (20 mL) was added, and the solution was extracted with Et_2O (3 × 10 mL). The organic layer was extracted with $NaHCO_3$ (satd aqueous, 10 mL). The aqueous layer is further extracted with Et_2O (2 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated to yield recovered (1*R*,2*S*,5*R*)-8-(*β*-naphthyl)-menthol (**28**, 86.3 mg, 90%). The H_2O layer was acidified to pH 2 with 6 N HCl and extracted with Et_2O (3 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to yield **20c** (48.5 mg, 62%): mp 168−170 °C $[\alpha]_D$ (≥96% ee) −13.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91−0.94 (t, J = 14.5 Hz, 3 H), 2.14−2.21 (m, 1 H), 2.45−2.52 (m, 1 H), 5.30 (d, J = 17.3 Hz, 1 H), 5.32 (d, J = 10.1 Hz, 1 H), 6.11−6.18 (dd, J = 10.8, 17.3 Hz, 1 H), 6.97 (s, 1 H), 7.43 (t, J = 7.65 Hz, 2 H), 7.51 (t, J = 7.26 Hz, 1 H), 7.80 (d, J = 7.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.2, 28.6, 77.2, 116.2, 127.1, 128.8, 132.0, 133.9, 136.2, 167.1, 174.8; IR (ATR) 3350−3440, 1750, 1652 cm^{-1}; MS (FAB 3-NBA + Li^+) 240 (M + Li^+), 160 (100), 136 (7); HRMS (FAB 3-NBA + Na^+) calcd for $C_{13}H_{15}NO_3Na$ (M + Na^+) 256.0949, obsd 256.0952.

***N*-Benzoyl-L-α-vinyl-*m*-tyrosine (20a).** From **19a** (298 mg, 0.43 mmol, mixture of α- to γ-alkylation products) following general procedure C was obtained **20a** (47.6 mg, 53%) and **28** (102 mg, 84%): mp 86−90 °C; $[\alpha]_D$ (88% ee) +11.3 (*c* 1.8, CD_3OD); ^{1}H NMR (500 MHz, CD_3OD) δ 3.43 (d, J = 13.3 Hz, 1 H), 3.53 (d, J = 13.3 Hz, 1 H), 5.27 (d, J = 10.8 Hz, 1 H), 5.32 (d, J = 17.3 Hz, 1 H), 6.16−6.23 (dd, J = 10.8, 17.3 Hz, 1 H), 6.61−6.64 (m, 3 H), 6.96−7.07 (m, 1 H), 7.40−7.45 (t, J = 7.04 Hz, 2 H), 7.52 (t, J = 7.26 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 41.9, 66.6, 115.8, 118.3, 122.6, 128.0, 128.1, 129.6, 130.0, 132.7, 136.0, 138.3, 138.6, 158.2, 169.4, 174.6; IR (ATR) 3489, 1700, 1684, 1559 cm$^{-1;}$ MS (FAB 3-NBA + Na^+) 334 (33, M + Na^+), 322 (50), 172 (100); HRMS (FAB 3-NBA + Na^+) calcd for $C_{18}H_{17}NO_4Na$ (M + Na^+) 334.1055, obsd 334.1051.

***N*-Benzoyl-L-α-vinylleucine (20b).** From **18** (200 mg, 0.38 mmol) following general procedure C, was obtained **20b** (73.5 mg, 74%) and **28** (98.6 mg, 92%): $[\alpha]_D$ (≥96% ee) −9.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, J = 7 Hz, 3 H), 0.93 (d, J = 7 Hz, 3 H), 1.71 (m, 1 H), 2.00−2.07 (dd, J = 7.5, 14 Hz, 1 H), 2.54−2.61 (dd, J = 5.5, 14 Hz, 1 H), 5.27 (d, J = 10.5 Hz, 1 H), 5.29 (d, J = 17 Hz, 1 H), 6.06−6.16 (dd, J = 10.5, 17 Hz, 1 H), 7.60 (s, 1 H), 7.42−7.47 (m, 2 H), 7.50−7.53 (m, 1 H), 7.80 (app d, J = 8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8, 23.8, 24.7, 43.2, 64.5, 115.6, 127.0, 128.7, 131.9, 134.2, 136.9, 166.6, 176.6; IR (ATR) 3294−3356, 1726, 1696, 1656 cm^{-1}; MS (EI) 261 (0.41 M$^{+)}$ 203 (13) 105 (100); HRMS (EI) calcd for $C_{15}H_{19}NO_3$ (M^+) 261.1365, obsd 261.13581.

***N*-Benzoyl-L-α-vinyllysine (20d).** From **25d** (115 mg, 0.21 mmol) following general procedure C, were obtained **20d** (45.5 mg, 78%) and **28** (52.1 mg, 87%). For purification, the solution was acidified with 10% HCl (15 mL), extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$), filtered, and evaporated to yield **20d**. After evaporation of the aqueous layer with mild heating (t ≤50 °C), the residue was applied to a Dowex 50 × 8 ion-exchange column. After the column was washed with several volumes of H_2O, elution with 1.3 M NH_4OH afforded **20d**: $[\alpha]_D$ (92% ee) +12.6 (*c* 1.2, D_2O); ^{1}H NMR (500 MHz, D_2O) δ 1.27−1.31 (m, 1 H); 1.35−1.40 (m, 1 H), 1.67−1.72 (m, 2 H), 2.09−2.15 (dt, J = 4.3, 12.9 Hz, 1 H), 2.38−2.44 (dt, J = 4.3, 12.9 Hz, 1 H), 2.98 (appt. t, J = 7.2 Hz, 2 H), 5.22 (d, J = 10.8 Hz, 1 H), 5.24 (d, J = 17.3 Hz, 1 H), 6.11−6.17 (dd, J = 10.8, 17.3 Hz, 1 H), 7.56−7.59 (m, 2 H), 7.64−7.67 (m, 1 H), 7.83−7.84 (m, 2 H); ^{13}C NMR (125 MHz, D_2O) δ 21.7, 27.5, 34.4, 40.0, 67.4, 114.5, 127.6, 129.7, 133.0, 134.8, 139.2, 169.5, 178.3; MS (FAB 3-NBA + Na^+) 299 (100, M + Na^+) 254 (13), 154 (9); HRMS (FAB 3-NBA) calcd for $C_{15}H_{20}N_2Na$ (M + Na^+) 299.1372, obsd 299.1365.

***N*-Benzoyl-L-α-vinylornithine (20e).** From **19e** (139 mg, 0.26 mmol) following general procedure C was obtained 1.7:1 mixture of **20e** (32.3 mg, 47%) and δ-lactam **29** (18.4 mg, 28%), as well as **28** (69.8 mg, 94%). For purification, the solution was acidified with 10% HCl (15 mL), extracted with Et_2O (3 × 15 mL). The organics were dried ($MgSO_4$), filtered, and evaporated to yield auxiliary **28**. The aqueous layer was then extracted with EtOAc (3 × 15 mL), dried ($MgSO_4$), filtered, and evaporated to yield **29**. After evaporation of the aqueous layer with mild heating (T ≤ 50 °C), the residue was applied to a Dowex 50 × 8 ion-exchange column. After the column was washed with several elutions of H_2O, elution with 1.3 M NH_4OH afforded **20e**: $[\alpha]_D$ (94% ee) +11.6 (*c* 1.5, D_2O); ^{1}H NMR (500 MHz, D_2O) δ 1.56−1.61 (m, 1 H), 1.66−1.71 (m, 1 H), 2.16−2.21 (dt, J = 4.4, 12.7 Hz, 1 H), 2.42−2.49 (dt, J = 4.4, 12.7 Hz, 1 H) 3.03 (appt. t, J = 7.6 Hz, 2 H), 5.25 (d J = 10.4 Hz, 1 H), 5.26 (d, J = 17.3 Hz, 1 H), 6.12−6.18 (dd, J = 10.4, 17.3 Hz, 1 H), 7.57 (t, J = 7.7 Hz, 2 H), 7.66 (t, J = 7.7 Hz, 1 H), 7.84 (app d, J = 7.7 Hz, 2 H); ^{13}C NMR (125 MHz, D_2O) δ 23.0, 31.8, 41.1, 67.0, 114.9, 127.6, 129.7, 133.1, 134.7, 138.9, 169.7, 177.8; MS (FAB 3-NBA) 263 (29 MH^+), 307 (100); HRMS (FAB 3-NBA) calcd for $C_{14}H_{18}N_2O_3$ (MH^+) 263.1395, obsd 263.1397.

For **29**: $[\alpha]_D$ −40.5 (*c* 0.6 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65−1.68 (m, 1 H), 1.86−1.89 (m, 1 H), 1.94−1.99 (m, 1 H), 2.82−2.34 (dt, J = 4.03, 13.3 Hz, 1 H), 2.77−2.80 (m, 1 H), 3.31−3.34 (m, 1 H), 3.44−3.49 (dt, J = 4.84, 11.2 Hz, 1 H), 5.35 (d, J = 10.8 Hz, 1 H), 5.38 (d, J = 17.3 Hz, 1 H), 6.01 (s, 1 H), 6.19−6.25 (dd, J = 10.4, 17.3 Hz, 1 H), 7.39 (t, J = 7.25 Hz, 2 H), 7.47 (t, J = 7.25 Hz, 1 H), 7.78 (app d, J = 7.25 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 30.7, 42.1, 61.1, 117.6, 127.0, 128.4, 131.5, 134.5, 137.3, 166.6, 171.5; IR (ATR) 3240−3252, 1601, 1559 cm^{-1}; MS (FAB 3-NBA) 245 (100 MH^+), 207 (44); HRMS (FAB 3-NBA) calcd for $C_{14}H_{16}N_2O_2$ (MH^+) 245.12903, obsd 245.1286.

Alternatively, a slight modification of general procedure C was used. Namely, to **19e** (65.6 mg, 0.12 mmol) were added KOtBu (120 mg, 1.1 mmol), H_2O (22 μL, 1.2 mmol), and 1,4-dioxane (1.6 mL) and this solution was heated for 18 h at 105 °C. Purification was carried out as above (without EtOAc extraction) to obtain **20e** (22.6 mg, 69%) and **28** (31.6 mg, 90%).

***N*-Benzoyl-L-α-vinylphenylalanine (20f).** From **17** (156 mg, 0.28 mmol) (1:1 mixture of α to γ), following general procedure C, were obtained **20f** (32.6 mg, 80% from α) and **28** (77.0 mg, 98%): $[\alpha]_D$ (82% ee) +12.4 (*c* 1.3, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.52 (d, 13.7 Hz, 1 H), 3.74 (d, *J* = 13.7 Hz, 1 H), 5.34 (d, *J* = 17 Hz, 1 H), 5.38 (d, *J* = 10.4 Hz, 1 H), 6.17−6.23 (dd, *J* = 10.4, 17 Hz, 1 H), 6.93 (s, 1 H), 7.17−7.19 (m, 2 H), 7.22−7.26 (m, 3 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.66 (app d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.4, 65.6, 116.8, 126.9, 127.2, 128.4, 128.7, 130.1, 131.9, 134.1, 135.2, 135.9, 167.4, 175.5; MS (EI) 295 (0.67, M^+), 204 (11), 105 (100); HRMS (EI) calcd for $C_{18}H_{17}NO_3$ (M^+) 295.1208, obsd 295.12099.

***N*-Benzoyl-L-α-vinylaspartate (20 g).** From **19g** (90 mg, 0.16 mmol), following general procedure C, were obtained **20g** (30.7 mg, 72%) and **28** (39.8 mg, 87%): ^{1}H NMR (300 MHz, CD_3OD) δ 3.27 (d, *J* = 16.4 Hz, 1 H), 3.52 (d, *J* = 16.4 Hz, 1 H), 5.24 (d, *J* = 10 Hz, 1 H), 5.32 (d, *J* = 17.3 Hz, 1 H), 6.11−6.21 (dd, *J* = 10, 17.3 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 2 H), 7.54 (t, *J* = 7.3 Hz, 1 H), 7.79 (app d, *J* = 7.3 Hz, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 40.2, 63.8, 116.1, 128.1, 129.6, 132.8, 135.9, 137.7, 168.7, 173.9; MS (FAB 3-NBA + Na^+) 286 (M + Na^+, 25), 413 (100); HRMS (FAB 3-NBA + Na^+) calcd for $C_{13}H_{13}NO_5Na$ (M + Na^+) 286.0691, obsd 286.0686.

***N*-Benzoyl-L-α-vinylvaline (20h).** From **19h** (112 mg, 0.22 mmol), following general procedure C, were obtained **20h** (40.9 mg, 76%) and **28** (49.5 mg, 80%): $[\alpha]_D$ (≥ 96% ee) −4.9 (*c* 0.9, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6 Hz, 3 H), 1.04 (d, *J* = 6 Hz, 3 H), 2.51 (app h, *J* = 7 Hz, 1 H), 5.20 (d, *J* = 17 Hz, 1 H), 5.33 (d, *J* = 10.5 Hz, 1 H), 6.29−6.35 (dd, *J* = 10.5, 17 Hz, 1 H), 6.62 (s, 1 H), 7.43−7.46 (t, *J* = 7.25 Hz, 2 H), 7.51−7.54 (t, *J* = 7.25 Hz, 1 H), 7.78−7.80 (app d, *J* = 7.25 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.1, 17.5, 34.5, 67.9, 115.8, 127.1, 128.8, 132.1, 133.6, 133.8, 167.7, 174.6; MS (EI) 203 (3.9 M^+-CO_2), 105 (100); HRMS (EI) calcd for $C_{14}H_{17}NO_3$ (M^+) 247.1208, obsd 203.12992 (M^+− CO_2).

***N*-Benzoyl-L-α-vinylnorvaline (20i).** From **19i** (83.0 mg, 0.16 mmol), following general procedure C, were obtained **20i** (31.5 mg, 78%) and **28** (32.6 mg, 72%): mp 91−94 °C; $[\alpha]_D$ (≥ 96% ee) −10.2 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91−0.94 (t, *J* = 7.25 Hz, 3 H), 1.19−1.26 (m, 1 H), 1.32−1.41 (m, 1 H), 2.05−2.11 (dt, *J* = 4.8, 13.7 Hz, 1 H), 2.46−2.52 (dt, *J* = 4.4, 13.3 Hz, 1 H), 5.28 (d, *J* = 10.4 Hz, 1 H), 5.31 (d, *J* = 17.3 Hz, 1 H), 6.10−6.16 (dd, *J* = 10.4, 17.3 Hz, 1 H), 7.14 (s, 1 H), 7.42−7.45 (t, *J* = 7.6 Hz, 2 H), 7.50−7.53 (t, *J* = 7.2 Hz, 1 H), 7.79−7.81 (d, 8.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) _ 13.9, 17.3, 37.2, 65.0, 115.8, 127.0, 128.7, 131.9, 134.1, 136.3, 166.8, 175.9. IR (ATR) 3313−3394, 1751, 1696, 1554 cm^{-1}; MS (FAB 3-NBA + Na^+) 270 (8,M + Na^+), 207 (43), 105 (100); HRMS (FAB 3-NBA + Na^+) calcd for $C_{14}H_{17}NO_3Na$ (M + Na^+) 270.1105, obsd 270.1097.

General Procedure D. L-α-Vinylbutyrine (21c). A suspension of **20c** (34.6 mg, 0.15 mmol) in 6 N HCl (1.11 mL) was heated at a reflux for 4 h. After extraction with CH_2Cl_2 (3 × 10 mL), the aqueous layer was evaporated in vacuo with mild heating (*T* ≤ 50 °C). The residue was applied to a Dowex 50 × 8 ion-exchange column. After the column was washed with several elutions of H_2O, elution with 1.3 M NH_4OH afforded **21c** (12.1 mg, 63%): mp 168−170 °C (≥96% ee); $[\alpha]_D$ +30.2 (*c* 0.6, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 1.00 (t, *J* = 7.25 Hz, 3 H), 1.91−1.96 (m, 1 H), 2.08−2.13 (m, 1 H), 5.37 (d, *J* = 17.7 Hz, 1 H), 5.45 (d, *J* = 11.3 Hz, 1 H), 6.09−6.15 (dd, *J* = 11.3, 17.7 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 8.0, 29.6, 66.9, 117.4, 136.3, 175.3; (FAB-glycerol) 130 (19, MH^+), 185 (100); HRMS (FAB glycerol) calcd for $C_6H_{11}NO_2$ (MH^+) 130.0868 obsd 130.0865.

L-α-Vinyl-*m*-tyrosine (21a). From **20a** (37.6 mg, 0.12 mmol), following general procedure D, was obtained **21a** (24.0 mg, 83%): $[\alpha]_D$ (88% ee) +7.9 (*c* 1.2 D_2O); ^{1}H NMR (500 MHz, D_2O) δ 3.15 (d, *J* = 14.1 Hz, 1 H), 3.46 (d, *J* = 14.1 Hz, 1 H), 5.43 (d, *J* = 17.7 Hz, 1 H), 5.56 (d, *J* = 10.8 Hz, 1 H), 6.19−6.25 (dd, *J* = 10.8, 17.7 Hz, 1 H), 6.78 (appt. s, 1 H), 6.71 (d, *J* = 7.65 Hz, 1 H), 6.89 (d, *J* = 7.25 Hz, 1 H), 7.29 (t, *J* = 8 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 41.9, 65.7, 116.0, 117.9, 119.2, 123.2, 131.3, 133.9, 135.2, 156.6, 172.5; MS (FAB 3-NBA) 208 (100, $M^{\bullet+}$); HRMS (FAB 3-NBA) calcd for $C_{11}H_{14}NO_2$ ($M^{\bullet+}$) 208.0974, obsd 208.0966.

L-α-Vinylleucine (21b). From **20b** (70.0 mg, 0.27 mmol), following general procedure D, was obtained **21b** (40.4 mg, 96%): $[\alpha]_D$ (≥96% ee) +26.3 (*c* 1.1, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 0.98 (d, *J* = 6 Hz, 3 H), 1.02 (d, *J* = 6 Hz, 3 H), 1.78 (m, 1 H), 1.83−1.87 (dd, *J* = 4.8, 14.9 Hz, 1 H), 2.01−2.05 (dd, *J* = 7, 14 Hz, 1 H), 5.36 (d, *J* = 17.7 Hz, 1 H), 5.42 (d, *J* = 10.8 Hz, 1 H), 6.12−6.17 (dd, *J* = 10.8, 17.7 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 23.0, 24.4, 45.0, 66.0, 116.5, 137.4, 175.5. (FAB-glycerol) 158 (100, MH^+), 112 (16), 93 (12); HRMS (FAB glycerol) calcd for $C_8H_{15}NO_2$ (MH^+) 158.1181, obsd 158.1174.

L-α-Vinyllysine (21d). From **20d** (32.5 mg, 0.12 mmol), following general procedure D, was obtained **21d** (14.5 mg, 71%): $[\alpha]_D$ (92% ee) +13.6 (*c* 0.7 D_2O); ^{1}H NMR (500 MHz, D_2O) δ 1.31−1.38 (m, 1 H), 1.45−1.53 (m, 1 H), 1.71−1.79 (m, 3 H), 1.95−2.01 (m, 1 H), 3.05 (t, *J* = 5.6 Hz, 2 H), 5.30 (d, *J* = 10.8 Hz, 1 H), 5.32 (d, *J* = 17.7 Hz, 1 H), 6.09−6.15 (dd, *J* = 10.8, 17.7 Hz, 1 H) ^{13}C NMR (500 MHz, D_2O) δ 21.3, 27.8, 37.7, 40.0, 65.0, 115.2, 140.0, 179.2; MS (FAB glycerol) 173 (100, $M^{\bullet+}$), 115 (8); HRMS (FAB glycerol) calcd for $C_8H_{17}N_2O_2$ ($M^{\bullet+}$) 173.1290, obsd 173.1286.

L-α-Vinylornithine (21e). From **20e** (30.1 mg, 0.11 mmol), following general procedure D, was obtained **21e** (17.7 mg, 96%): $[\alpha]_D$ (94% ee) +18.8 (*c* 0.8, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 1.56−1.62 (m, 1 H), 1.66−1.74 (m, 2 H), 1.88−1.95 (m, 2 H), 2.97 (appt. t, *J* = 17.7 Hz, 2 H), 5.22 (d, *J* = 10.8 Hz, 1 H), 5.25 (d, *J* = 17.7 Hz, 1 H), 6.03−6.08 (dd, *J* = 10.8, 17.7 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 22.9, 35.4, 40.2, 64.4, 115.0, 140.4, 179.6; MS (FAB 3- NBA) 159 (100 $M^{\bullet+}$), HRMS (FAB 3-NBA) calcd for $C_7H_{15}N_2O_2$ ($M^{\bullet+}$) 159.1133, obsd 159.1139.

21e (6.0 mg, 83%) was also obtained from **29** (11.1 mg, 0.05 mmol) following a slight modification of general procedure D, in which the reaction was done in a pressure vessel for 10 h at 105 °C.

L-α-Vinylphenylalanine (21f). From **20f** (42.5 mg, 0.14 mmol), following general procedure D, **21f** was obtained (18.5 mg, 85%): mp 212−214 °C; $[\alpha]_D$ (82% ee) +13.1 (*c* 0.8, MeOH); ^{1}H NMR (500 MHz, D_2O) δ 3.09 (d, *J* = 14.1 Hz, 1 H), 3.42 (d, *J* = 14.1 Hz, 1 H), 5.31 (d, *J* = 17.7 Hz, 1 H), 5.42 (d, *J* = 10.8 Hz, 1 H), 6.16−6.22 (dd, *J* = 10.8, 17.7 Hz, 1 H), 7.27−7.29 (m, 2 H), 7.36−7.41 (m, 3 H); ^{13}C NMR (125 MHz, D_2O) δ 42.0, 66.8, 117.3, 128.6, 129.6, 130.8, 134.2, 135.8, 174.3; MS (FAB 3-NBA) 192 (100 M^+) 146 (33); HRMS (FAB 3-NBA) calcd for $C_{11}H_{14}NO_2$ (M^+) 192.1024, obsd 192.1023.

L-α-Vinylaspartate (21 g). From **20g** (30.0 mg, 0.11 mmol), following general procedure D, was obtained **20g** (21.9 mg, 98%): $[\alpha]_D$ (≥96% ee) +37.5 (*c* 0.9, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 3.09 (d, *J* = 18 Hz, 1 H), 3.38 (d, *J* = 18 Hz, 1 H), 5.56 (d, *J* = 17.7 Hz, 1 H), 5.59 (d, *J* = 10.8 Hz, 1 H), 6.05−6.11 (dd, *J* = 10.8, 17.7 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 39.6, 62.9, 120.2, 133.3, 172.8, 174.1; MS (FAB-glycerol) 160 (100, MH^+), 158 (55), 130 (31), 115 (32); HRMS (FAB glycerol) calcd for $C_6H_9NO_4$ (MH^+) 160.0609, obsd 160.0605.

L-α-Vinylvaline (21h). From **20h** (16.6 mg, 0.07 mmol), following general procedure D, was obtained **20h** (11.1 mg, 97%): $[\alpha]_D$ (≥96% ee) +30.7 (*c* 0.6, D_2O); ^{1}H NMR δ (500 MHz, D_2O) δ 0.95 (d, *J* = 7.25 Hz, 3 H), 0.96 (d, *J* = 7.25 Hz, 3 H), 2.39−2.41 (h, *J* = 7.25 Hz, 1 H), 5.31 (d, *J* = 17.7 Hz, 1 H) 5.46 (d, *J* = 11.2 Hz, 1 H), 6.14−6.17 (dd, *J* = 11.2, 17.3 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 16.2, 17.1, 33.8, 70.5, 116.5, 136.3, 175.0; MS (FAB glycerol) 144 (100, MH^+), 115 (13); HRMS (FAB glycerol) calcd for $C_7H_{13}NO_2$ (MH^+) 144.10243, obsd 144.1023.

(1″*R*,2″*S*,5″*R*)-8″-(β-Naphthyl)menthyl *N*-Benzoyl-L-α-(4′-iodo)butyl-α-vinylglycinate (22d). To a solution of **19d** (400 mg, 0.71 mmol) in acetone (9.7 mL) was added NaI (dried prior to use, 200 °C in vacuo) (429 mg, 2.85 mmol), and the

solution was heated to 40 °C for 7 d. After evaporation of the acetone, the residue was taken up in Et_2O (25 mL), extracted with 1 M sodium thiosulfate (3 × 20 mL), dried ($MgSO_4$), evaporated, and chromatographed (10% EtOAc/hexane) to yield **22d** (435 mg, 93%): $[\alpha]_D$ (92% de) +7.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500, $CDCl_3$) δ 0.83−0.92, (m, 1 H), 0.89 (s, 3 H), 1.03−1.27 (m, 2 H), 1.29−1.32 (m, 1 H), 1.31 (s, 3 H), 1.40 (s, 3 H), 1.42−1.57 (m, 4 H), 1.69−1.84 (m, 3 H), 2.10−2.12 (m, 1 H), 2.17−2.22 (m, 1 H), 2.38−2.44 (dt, *J* = 4.4, 13 Hz, 1 H), 3.04−3.09 (m, 1 H), 3.13−3.18 (m, 1 H), 4.93−4.98 (dt, *J* = 4.0, 10.4 Hz, 1 H), 5.10 (d, *J* = 10.4 Hz, 1 H), 5.19 (d, *J* = 17 Hz, 1 H), 5.58−5.64 (dd, *J* = 10.4, 17 Hz, 1 H), 7.10 (s, 1 H), 7.41−7.54 (m, 7 H), 7.62−7.64 (m, 1 H), 7.72−7.79 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 24.7, 25.7, 27.3, 28.5, 31.5, 32.9, 33.1, 34.4, 40.2, 41.6, 49.6, 64.8, 77.3, 78.2, 115.7, 123.4, 124.8, 125.3, 125.9, 126.9, 127.2, 127.3, 127.6, 127.9, 128.6, 131.6, 133.4, 134.8, 135.8, 148.1, 165.7, 171.8; IR (ATR) 3310−3400, 1718, 1671 cm^{-1}; MS (FAB 3-NBA) 652 (50, MH^+) 388 (100), 169, (96); HRMS (FAB 3-NBA) calcd for $C_{35}H_{42}NO_3I$ (MH^+) 652.2287, obsd 652.2291.

(1″*R*,2″*S*,5″*R*)-8″-(*β*-Naphthyl)menthyl *N*-Benzoyl-α-(4′-azido)butyl-L-α-vinylglycinate (23d). NaN_3 (59.8 mg, 0.92 mmol) and 15-crown-5 (13.5 mg, 60 μmol) were added to a solution of **22d** (400 mg, 0.61 mmol) in DMF (6.7 mL), and the solution was heated to 70 °C for 5 h. After cooling, the solution was taken up in Et_2O (25 mL) and extracted with H_2O (3 × 25 mL), dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (10% EtOAc/hexane) yielded **23d** (316 mg, 91%): $[\alpha]_D$ (92% de) +3.6 (*c* 1.00 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ0.81−0.87 (m, 1 H), 0.89 (s, 3 H), 1.03−1.15 (m, 2 H), 1.21−1.29 (m, 2 H), 1.32 (s, 3 H), 1.41 (s, 3 H), 1.42−1.61 (m, 5 H), 1.79−1.85 (dt, *J* = 4.4, 13.3 Hz, 1 H), 2.07−2.09 (m, 1 H), 2.17−2.22 (dt, *J* = 3.23, 12.0 Hz, 1 H), 2.36−2.42 (dt, *J* = 4.8, 13.3 Hz, 1 H), 3.13−3.19 (m, 1 H), 3.21−3.26 (m, 1 H), 4.93- -4.98 (dt, *J* = 4.4, 10 Hz, 1 H), 5.10 (d, *J* = 10.4, 1 H), 5.20 (d, *J* = 17.3, 1 H), 5.59−5.66 (dd, *J* = 10.4, 17.3 Hz, 1 H), 7.09 (s, 1 H), 7.40−7.47 (m, 5 H), 7.49−7.53 (m, 2 H), 7.64 (br s, 1 H), 7.72 (d, *J* = 8.8 Hz, 1 H), 7.76−7.79 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.7, 25.7, 27.3, 28.4, 28.5, 31.3, 33.4, 34.3, 40.2, 41.4, 49.6, 51.0, 64.8, 78.2, 115.7, 123.4, 124.7, 125.3, 125.9, 126.9, 127.2, 127.3, 127.5, 127.8, 128.5, 131.5, 133.4, 134.7, 135.8, 148.1, 165.7, 171.8; IR (ATR) 3320−3410, 2142, 1751, 1700 cm^{-1}. Anal. Calcd for $C_{35}H_{42}N_4O_3$: C, 74.17; H, 7.46; N, 9.89. Found: C, 74.19; H, 7.07, N, 9.96.

(1″*R*,2″*S*,5″*R*)-8″-(*β*-Naphthyl)menthyl *N*-Benzoyl-L-α-[4′-imino-(triphenylphosphino)]butyl-α-vinylglycinate (24d). To a solution of **23d** (239 mg, 0.42 mmol) in toluene (2.5 mL) was added triphenylphosphine (309 mg, 1.18 mmol) and the solution was heated to 110 °C for 72 h. After evaporation of the crude **24d** was obtained.

(1′*R*,2′*S*,5′*R*)-8′-(*β*-Naphthyl)menthyl *N*-Benzoyl-L-α-vinyllysinate (25d). 24d was suspended in 3 N HCl and heated to 60 °C for 32 h. After cooling, the reaction mixture was taken up in 1 N Na_2CO_3 (25 mL), extracted with Et_2O (3 × 25 mL), dried (Na_2SO_4), filtered, and evaporated. Chromatography was carried out initially with 20% EtOAc/hexane and then with 5% MeOH/CH_2Cl_2 [(1% NH_4OH (satd aq)] yields **25d** (126 mg, 55% over two steps): $[\alpha]_D$ (92% de) +0.40 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78−0.83 (m, 1 H), 0.87 (d,*J* = 6.4 Hz, 3 H), 1.0−1.08 (m, 2 H), 1.32 (s, 3 H), 1.40 (s, 3 H), 1.21−1.37 (m, 4 H), 1.39−1.55 (m, 5 H), 1.79−1.85 (dt, *J* = 4.03, 14.3 Hz, 1 H), 2.04−2.07 (m, 1 H), 2.13−2.18 (dt, *J* = 3.2, 12.0, 1 H), 2.35−2.41 (dt, *J* = 4.8, 13.2 Hz, 1 H), 2.59−2.63 (m, 2 H), 4.92−4.97 (dt, *J* = 4.0, 10.8 Hz, 1 H), 5.08 (d, *J* = 10.8 Hz, 1 H), 5.19 (d, *J* = 17.3 Hz, 1 H), 5.65−5.71 (dd, *J* = 10.8, 17.3 Hz, 1 H), 7.10 (s, 1 H), 7.39−7.51 (m, 7 H), 7.62 (app s, 1 H), 7.70−7.79 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.6, 25.4, 27.2, 28.6, 31.2, 33.2, 33.9, 34.3, 40.1, 41.4, 41.7, 49.5, 64.8, 77.8, 115.3, 123.3, 124.7, 125.2, 125.8, 126.9, 127.2, 127.5, 127.8, 128.4, 131.4, 131.4, 133.2, 134.7, 135.8, 148.0, 165.6, 171.9. IR (ATR) 3310−3370, 1700, 1669, 1580 cm^{-1}. Anal. Calcd for $C_{35}H_{44}N_2O_3$: C, 77.74; H, 8.20; N, 5.18. Found: C, 77.88; H, 7.89; N, 4.99.

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Supporting Information Available: Detailed synthetic procedures and spectral characterization data for compounds **2**−**9** and copies of ^{1}H NMR spectra for compounds **2**, **3**, **6**−**18**, **19a**,**c**−**e**,**g**−**j**, **20a**−**i**, **21a**−**h**, **22d**, **23d**, **25d**, **26**, **27**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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