Enantiomerically Enriched α-Methyl Amino Acids. Use of an Acyclic, Chiral Alanine-Derived Dianion with a High Diastereofacial Bias†

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Hindered esters derived from *N*-benzoylalanine and the following chiral alcohols have been synthesized: (1) (−)-isopinocampheol, (2) (−)-*trans*-2-phenylcyclohexanol, and (3) (−)-8-phenylmenthol. Sequential treatment of these esters with LDA (1.2 equiv) and *n*-butyllithium (2.4 equiv) at −78 °C in THF generates the corresponding chiral dianions. Alkylation of each of these with benzyl bromide reveals that only the (−)-8-phenylmenthyl auxiliary confers a high diastereofacial bias upon its derivative dianion. In fact, that dianion (**6**) consistently displays diastereomeric ratios in the range of 89:11 to 94:6 for alkylations with a spectrum of nine alkyl halides. If one recrystallization step is included, a single diastereomeric product may be obtained, as is demonstrated for the benzylation of **6**. Of particular note, the alkylation with 3,4-bis((*tert*-butyldimethylsilyl)oxy)benzyl bromide (**18**) (94:6 diasteriomeric ratio, 72% yield) constitutes a formal synthesis of the clinically important antihypertensive (*S*)-α-methyl-DOPA (Aldomet), in enantiomerically enriched form. In all cases studied, yields are markedly improved, yet diastereoselectivities unchanged, by the addition of 10% HMPA to the reaction milieu. The (−)-8-phenylmenthol chiral auxiliary is conveniently recovered via ester cleavage with KO_2/18-crown-6, following alkylation. Complete deprotection affords enantiomerically enriched (*S*)-α-methyl amino acids, in all cases examined, indicating that dianion **6** displays a substantial bias in favor of *si* face alkylation. This sense of diastereoselection is consistent with a chain-extended, internal chelate model for the reactive conformation of the dianion.

Introduction

Owing to their biological properties, both as free amino acids and as components of peptides, and to their conformational properties, α-methyl amino acids have assumed an important role in bioorganic chemistry in recent years. For example, (*S*)-α-methyl-DOPA (Aldomet), an inhibitor of DOPA decarboxylase, is an important commercial antihypertensive.[1] Substitution of (*S*)-α-methyltyrosine for tyrosine-4 in angiotensin II results in a peptide that is resistant to chymotryptic degradation, yet retains 93% of the pressor activity of the parent peptide.[2] In the *de novo* design of peptides and proteins, several chiral α-methyl amino acids are useful building blocks for engineering helical secondary structure. For instance, (*S*)-isovaline (α-methylbutyrine) has been used to construct peptides with a 3_{10} helical structure.[3a] On the other hand, (*R*)-α-methylaspartate is an especially effective building block for engineering α-helical structure.[3b]

For all of these applications, optically pure α-methyl amino acids are desirable. One direct synthetic approach to these compounds involves the α-alkylation of a chiral alanine equivalent. This approach has, of course, been reduced to practice with the development of several cyclic,[4] chiral alanine-derived monoanions which display a very high diastereofacial bias. Perhaps most notable among these are the bis-lactim ether of Schöllkopf,[5] the imidazolidinones and oxazolidinones due to Seebach (self-reproduction of chirality),[6] and the diphenyloxazinones developed by Williams.[7] Ojima has also reported an acyclic[4] chiral alanine enolate, in which chelation is elegantly used to control enolate geometry, and for which the chiral element resides exclusively in a β-lactam ring containing the α-amino group.[8,9] The impressive diastereoselectivities recorded in these systems notwithstanding, a potential drawback to these approaches lies in the fact that, with one exception,[10] the chiral directing element is destroyed in the process of deprotection.

We recently reported a general procedure for the

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(2) Khosla, A.; Stachowiak, K.; Smeby, R. R.; Bumpus, F. M.; Piriou, F.; Lintner, K.; Fermandjian, S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 757–760.

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(4) These chiral alanine equivalents are "cyclic" in the sense that, in each case, the carboxyl and amino group are joined together in a cyclic manner as part of a four- to six-membered ring.

(5) (a) Schöllkopf, U.; Busse, U.; Lonsky, R.; Hinrichs, R. *Liebigs Ann. Chem.* **1986**, 2150–2163. (b) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085–2091. (c) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799–1806. (d) Schöllkopf, U.; Hausberg, H.-H.; Segal, M.; Reiter, U.; Hoppe, I.; Saenger, W.; Lindner, K. *Liebigs Ann. Chem.* **1981**, 439–458.

(6) (a) Seebach, D.; Gees, T.; Schuler, F. *Liebigs Ann. Chem.* **1993**, 785–799. (b) Altmann, E.; Nebel, K.; Mutter, M. *Helv. Chim. Acta* **1991**, *74*, 800–806. (c) Seebach, D.; Dziadulewicz, E.; Behrhardt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215–1232. (d) Gander-Coquoz, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 224–236. (e) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277–5292. (f) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194–1216. (g) Fadel, A.; Salaün, J. *Tetrahedron Lett.* **1987**, *28*, 2243–2246. (h) Seebach, D.; Aebi, J. D. *Helv. Chim. Acta* **1985**, *68*, 1507–1518. (i) Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144–154. (j) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243–1250. (k) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545–2548. (l) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.

(7) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11–25. (b) Williams, R. M.; In, M.-N. *J. Am. Chem. Soc.* **1991**, 113, 9276.

(8) (a) Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307–5318. (b) Colson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918–5924.

(9) For detailed reviews, see: (a) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238. (b) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, 1989; Vol. 7.

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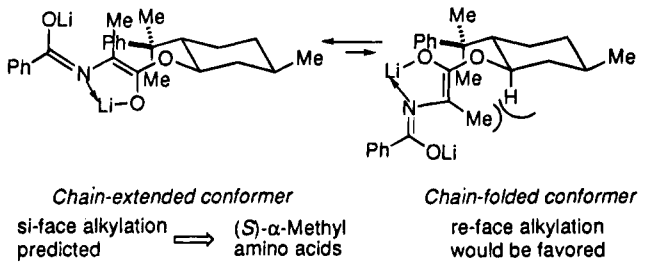
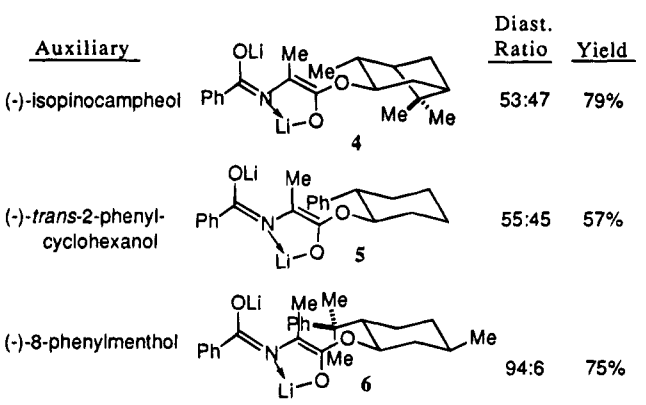
Scheme 1



synthesis of racemic, α-vinyl amino acids via the formal vinylation of the parent amino acids. The key step in this procedure is the regiospecific, α-alkylation of *N*-benzoylamino ester-derived dianions[11] with ethylene oxide as vinyl cation equivalent.[12] As a first step toward developing an asymmetric version of that chemistry, we set out to explore the behavior of analogous chiral dianions, in which all stereochemical information resides in the alcoholic component of the ester functionality. In particular, we chose to investigate chiral alanine-derived dianions initially, as diastereoselective alkylation of these would provide a direct route to enantiomerically enriched α-methyl amino acids, with the possibility of readily recycling the chiral auxiliary.

Our strategy was based upon the following premises. It is likely that dianions derived from *N*-benzoyl-α-amino esters assume an internal chelate structure, in which the electron-rich amide nitrogen enters into a five-ring chelate with the lithium counterion ion of the ester, allowing for control of enolate geometry. It is further presumed that dianions of this type, bearing an auxiliary of the *trans*-2-alkylcyclohexyl variety, will prefer a chain-extended conformation over a chain-folded conformation, for steric reasons, as is illustrated in Scheme 1. Finally, if alkylations proceed largely through this chain-extended conformer, substantial diastereofacial selectivity is expected, provided that the 2-substituent is an effective shielding group. It is important to note that Newcomb and Bergbreiter first described the behavior of one such "chiral alanine dianion" a decade ago.[13] In that work, the dianion of *N*-benzoylalanine (−)-menthyl ester was alkylated with three alkyl halides to produce protected α-methyl amino acids with modest diastereofacial selectivity 20−48% de [60:40−74:26 diasteriomeric ratios]. One is led to conclude that if the internal chelate, chain-extended model (as illustrated in Scheme 1) correctly represents the reactive conformation of the dianion, then the menthyl blocking group (isopropyl) does not effectively screen the *re* face of the dianion. One could further surmise that by changing the nature of the blocking group one might be able to obtain high diastereofacial selectivity in the alkylation of acyclic chiral alanine dianions of this type. Following this working hypothesis, we set about to systematically vary the structure of the chiral auxiliary and examine its effect on diastereoselectivity.

Scheme 2. Acyclic Chiral Alanine Dianions: Diastereofacial Biases



We chose the inexpensive and readily available alcohol, (−)-isopinocampheol, as a base line auxiliary for these studies. As illustrated in Scheme 2, one expects very limited face-shielding with this auxiliary. On the other hand, given the impressive diastereoselectivities observed by Ojima and Georg[14] with the enolate monoanions of Whitesell [(−)-*trans*-2-phenylcyclohexyl] esters in the ester enolate−imine cyclocondensation, this auxiliary appeared to be an obvious candidate, for which substantial diastereofacial shielding might be expected (Scheme 2). Finally, we chose the (−)-8-phenylmenthol (Corey) auxiliary[15] to assess the effect of inserting a one-carbon spacer between the cyclohexane ring and phenyl group upon diastereofacial bias of the alanine dianion.

Results and Discussion

The desired hindered esters **1**−**3** were obtained in nearly quantitative yield by simple fusion of *N*-benzoylalanyl chloride[16] with 1 equiv of isopinocampheol, *trans*-2-phenylcyclohexanol, or 8-phenylmenthol, respectively, at 75 °C.[17] This alcohol/*N*-benzoylamino acid chloride fusion method (98% yield, 1 h reaction time, for the phenylmenthyl ester of *N*-benzoylalanine) is clearly superior to the Harada procedure [TsOH, Dean-Stark trap: 58−79% yield, 30 h reaction time, for the (less hindered) menthyl ester of alanine][18] that is typically employed to synthesize hindered esters of amino acids.[13]

To define the relative diastereofacial biases of dianions **4**−**6**, each of these was subjected to alkylation with

(10) In the case of the Schöllkopf chiral alanine equivalent,[5] (*R*)- or (*S*)-valine methyl ester may be recovered in the deprotection procedure and used to recontruct the bis-lactim ether, in several steps.[5a]

(11) Krapcho, A. P.; Dundulis, E. A. *Tetrahedron Lett.* **1976**, 2205−2208.

(12) (a) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966−6975. (b) Pedersen, M. L.; Berkowitz, D. B. *Tetrahedron Lett.* **1992**, *33*, 7315−7318.

(13) (a) Davenport, K. D.; Mao, D. T.; Richmond, C. M.; Bergbreiter, D. E.; Newcomb, M. *J. Chem. Res., Synop.* **1984**, 148−149; *J. Chem. Res., Miniprint* **1984**, 1518−1530. (b) Note: In the course of this work, a "reinvestigation" of the Bergbreiter/Newcomb study appeared: McIntosh, J. M.; Thangarasa, R.; Foley, N. K.; Ager, D. J.; Froen, D. E., Kix, R. C. *Tetrahedron* **1994**, *50*, 1967−1974. These workers alkylated chiral *N*-benzoylglycine-derived dianions, including one example with a phenylmenthyl auxiliary. No alkylations leading to quaternary centers and, hence, to α-branched amino acids were reported.

(14) Ojima, I.; Habus, I.; Zhao, M.; Georg, G.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681−1683.

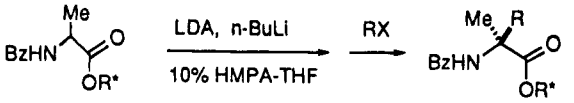
(15) For a thorough review of the use of this and related auxiliaries, see: Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953−964.

(16) Max, J. *Liebigs Ann. Chem.* **1909**, *369*, 276−286.

(17) In all three cases, starting from optically pure *N*-benzoyl-(*S*)-alanine, a mixture of diastereomeric esters, epimeric at the α-center, is obtained. The fact that the diastereomeric ratio varied from 1:1 to 2.2:1 (α-*S*:α-*R*), as function of the chiral alcohol, argues against racemization of the acid chloride as a likely mechanism for the observed loss of stereochemical integrity. Indeed, these results raise the interesting possibility that esterification may proceed via the initial generation of a ketene upon thermolysis of the amino acid chloride. At any rate, the fact that diastereomeric esters are obtained in this step is of no consequence here.[21]

(18) Harada, K.; Hayakawa, T. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 191−194.

Table 1. Enantiomerically Enriched α-Methyl Amino Acids[a]



RX	protected amino acid	yield (%)	diast ratio[d]
$PhCH_2Br$	α-methylphenylalanine (**9**)	75	94:6 (≥99:1)[e]
CH_3CH_2I	isovaline[c] (α-methylbutyrine) (**10**)	68	93:7
t-BuO_2CCH_2Br	α-methylaspartate (**11**)	86	91:9
$PhCH_2OCH_2Br$	α-methylserine[c] (**12**)	77	89:11
$PhCH{=}CHCH_2Br$	α-methylcinnamylglycine[c] (**13**)		
$HCCCH_2Br$	α-methylpropargylglycine[c] (**14**)	67	93:7
$H_2C{=}CHCH_2Br$	α-methylallylglycine[c] (**15**)	69	94:6
$(CH_3)_2CHCH_2I$	α-methylleucine (**16**)	86	89:11
$ArCH_2Br$[b]	α-methyl-DOPA[c] (**19**)	72	94:6

[a] R*OH = (−)-8-phenylmenthol. [b] Ar = 3,4-bis((*tert*-butyldimethylsilyl)oxy)phenyl. [c] Reference 24. [d] Reference 22. [e] After a single recrystallization (68% recrystallized yield).

benzyl bromide.[19-21] Not surprisingly, the isopinocampheol auxiliary produced little diastereoselection. On the other hand, rather unexpectedly,[14] the (−)-8-phenylmenthol-derived dianion **6** showed a much greater diastereofacial bias than the *trans*-2-phenylcyclohexanol-derived dianion **5** (Scheme 2).[22] This initial screening result led us to pursue alkylations with dianion **6** and a considerable variety of alkyl halides.

Initially, we performed these alkylations in the absence of HMPA and obtained the following yields (single runs, indexed by electrophile): benzyl bromide (32%), *tert*-butyl bromoacetate (48%), benzyloxymethyl bromide (64%), cinnamyl bromide (44%), propargyl bromide (33%), allyl bromide (56%), and isobutyl iodide (18%). As can be seen from Table 1, in the presence of 10% HMPA, yields are significantly improved for the alkylation of dianion **6** with all alkyl halides surveyed, including the relatively hindered electrophile, isobutyl iodide. *In all cases, the observed diastereomeric ratios were the same as those obtained in the absence of HMPA.* This result is of practical utility and contrasts strikingly with recent reports of alkylations with related enolates, for which high diastereoselectivities were only achievable (i) by limiting the amount of additive (HMPA or TMEDA) to stoichiometric quantities[13b] or (ii) by resorting to the use of expensive, non-lithium bases.[23]

Employing this procedure, one can synthesize a considerable variety of protected, α-methyl amino acids in diastereomeric ratios of 89:11−94:6 (78−88% de) by alkylation of dianion **6** with the appropriate alkyl halide. Moreover, with the inclusion of a single recrystallization step, one can obtain enantiomerically pure α-methyl amino acids, as has been demonstrated for (*S*)-α-methylphenylalanine.

The absolute stereochemistry of the alkylation products has been determined unambiguously in three cases (α-methylphenylalanine, α-methylleucine and α-methylaspartate) by hydrolysis (9 N HCl, reflux) of the alkylation products directly to the corresponding free, α-methyl amino acids.[24,25] Comparison of the optical rotations of these with literature values indicates that, at least in these cases, the absolute stereochemistry of the predominant enantiomer is (*S*), in agreement with the chain-extended, internal chelate model proposed for the reactive dianion conformation (Scheme 1).

While refluxing the alkylation products in aqueous HCl results in the hydrolysis of both the ester and amide protecting groups in a single step, it also leads to destruction of the chiral auxiliary. On the other hand, the (−)-8-phenylmenthol auxiliary may be conveniently recovered in good yield via ester cleavage with KO_2/18-crown-6,[26] following alkylation (Scheme 3). This represents an important potential practical advantage of the "chiral alanine" alkylation procedure described here over existing alternatives.[5-9]

In summary, alkylation of the acyclic, chiral alanine-derived dianion **6** with alkyl halides provides a convenient and direct procedure for the synthesis of enantiomerically enriched (78−88% ee without recrystallization, 100% ee possible with a single recrystallization) (*S*)-α-methyl amino acids. The sense of diastereoselection observed is consistent with a chain-extended, internal chelate model for the reactive conformation of the dian-

(19) Attempts to deprotonate **2** with excess LDA (>5 equiv) at −78 °C resulted in incomplete deuterium incorporation at the α-position upon quenching with d_4-methanol−DCl.[20] By contrast, deprotonation of **1**−**3** by sequential treatment with LDA (1 equiv, to deprotonate the amide NH) and *n*-butyllithium (2 equiv, to deprotonate both the diisopropylamine produced and the α-proton) at −78 °C led to complete incorporation of deuterium at C_α, using the same quench. Therefore, this latter deprotonation procedure was also employed for all alkylation reactions of **4**−**6**.

(20) Seebach and co-workers have shown that diisopropylamine molecules may be hydrogen-bonded to the α-C-atoms of certain LDA-derived enolates, in the crystal. Upon quenching such enolates with an acidic deuterium source, internal proton delivery from associated diisopropylamine molecules may effectively compete with external delivery of deuterium from the quenching agent, resulting in incomplete labeling. We cannot rule out that such a mechanism is operative here. See: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654. (b) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373−1393.

(21) As a control experiment, dianion **6** was generated by deprotonation of (i) the major diastereomer (**3a**, see Experimental Section), of (ii) the minor diastereomer **3b**, and of (iii) the diastereomeric mixture (**3a/3b**). In each case, subsequent alkylation with benzyl bromide produced **9** in ca. 75% yield, as a 94:6 mixture of diastereomers.

(22) Diastereomeric ratios were determined by integration of resolved signals in the ^1H NMR spectra of the diastereomeric mixtures. In all cases examined, these were in very good agreement with the enantiomeric ratios obtained (from optical rotations) for the fully deprotected α-methyl amino acids.

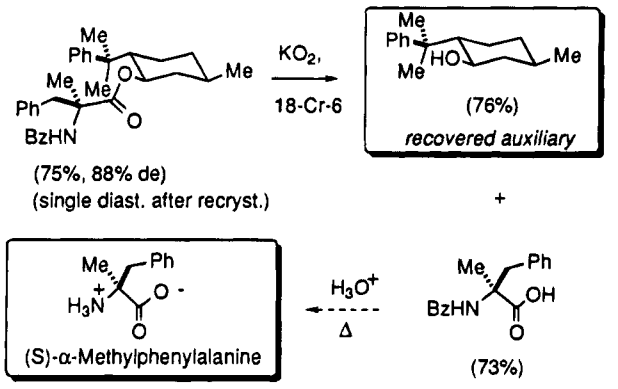
(23) Solladié-Cavallo, A.; Csaky, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem.* **1994**, *59*, 5343−5346.

(24) In these cases, stereochemistry at C_α is presumed to be *S*, by analogy with the cases of α-methylphenylalanine, α-methylleucine, and α-methyl aspartate, for all of which the *S* isomer is produced.

(25) The yields obtained here for the simultaneous cleavage of the N-benzamide and the hindered ester protecting groups are quite modest (ca. 40−60%; see Experimental Section). In contrast, typical yields for the cleavage of an *N*-benzoyl- or *N*-acetylamino protecting group from unhindered esters of α-branched amino acids are in the 70−90% range [See: (a) ref 12a. (b) Saito, H.; Tahara, Y.; Toyoda, M. *Agric. Biol. Chem.* **1988**, *52*, 2349−2350. (c) Pines, S. H.; Karady, S.; Kozlowski, M. A.; Sletzinger, M. *J. Org. Chem.* **1968**, *33*, 1762−1767].

(26) Buschmann, H.; Scharf, H.-D. *Synthesis* **1988**, 827−830.

Scheme 3



ion. We also note that the enantiomeric auxiliary, (+)-8-phenylmenthol, can be readily synthesized from (−)-citronellal,[27] and so the methodology described herein could readily be applied to the synthesis of (*R*)-α-methyl amino acids,[3b] as well. Of particular significance, the alkylation with 3,4-bis((*tert*-butyldimethylsilyl)oxy)benzyl bromide (**18**) constitutes a formal synthesis of the important antihypertensive, (S)-α-methyl-DOPA (Aldomet), in enantiomerically enriched form. In all cases studied, yields are markedly improved, yet diastereoselectivities unchanged, by the addition of 10% HMPA to the reaction milieu. Furthermore, the (−)-8-phenylmenthol auxiliary can be efficiently recycled by cleavage of the product ester with KO_2/18-crown-6 in benzene.

Experimental Section

General. All general experimental procedures were as described previously.[12] For the labeling studies,[19] percent α-deuterium incorporation was determined by GC/MS (HP-5890 gas chromatograph with an HP-5972 mass spectral detector). All CI-mass spectra reported herein were obtained using this instrument. *n*-Butyllithium in hexanes (nominally 1.6 M) was purchased from Aldrich and titrated[28] before each use.

General Procedure A. (1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-(*S*)-alaninate (3a)/(1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-(*R*)-alaninate (3b). A mixture of (−)-8-phenylmenthol[29] (3.00 g, 12.9 mmol) and *N*-benzoylalanyl chloride[16] (3.01 g, 14.2 mmol; freshly prepared from *N*-benzoyl-L-alanine) was heated to 78 °C for 1 h. The crude product was partitioned between EtOAc (25 mL) and $NaHCO_3$ (aqueous, 30 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (15% EtOAc/hexanes) provided **3b** (1.64 g, 31%), as a white solid, in a first fraction, and **3a** (3.52 g, 67%) also as a white solid, in a second fraction.

3a: mp 98−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78−1.59 (m, 6 H), 0.86 (d, *J* = 6 Hz, 3 H), 1.23 (s, 3 H), 1.33 (d, *J* = 7 Hz, 3 H), 1.33 (s, 3 H), 1.93−1.96 (m, 1 H), 2.02−2.07 (app dt, *J* = 4, 12 Hz, 1 H), 4.43 (app quintet, *J* = 7 Hz, 1 H), 4.92 (app dt, *J* = 4, 10.5 Hz, 1 H), 6.52 (d, *J* = 7 Hz, 1 H), 7.09−7.11 (m, 1 H), 7.20−7.27 (m, 4 H), 7.41−7.45 (m, 2 H), 7.48−7.51 (m, 1 H), 7.74−7.76 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 21.6, 26.1, 27.0, 27.5, 31.3, 34.4, 40.0, 41.6, 49.1, 50.0, 76.6, 125.4, 125.5, 127.0, 128.0, 128.5, 131.5, 134.2, 150.7, 166.6, 172.1; MS (methane − CI) 448 (0.2, M + 41), 436 (0.4, M + 29), 408 [2.4, (M + H)$^+$], 194 (100), 176 (9.9), 105 (34). Anal. Calcd for $C_{26}H_{33}NO_3$: C, 76.63; H, 8.16; N, 3.44. Found: C, 76.84; H, 8.41; N, 3.51.

3b: mp 98−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87−1.13 (m, 3 H), 0.90 (d, *J* = 7 Hz, 3 H), 1.22 (s, 3 H), 1.24 (d, *J* = 7 Hz, 3 H), 1.33 (s, 3 H), 1.47−1.53 (m, 1 H), 1.68−1.72 (m, 1 H), 1.78−1.87 (m, 2 H), 2.06−2.09 (app dt, *J* = 4, 12 Hz, 1 H), 4.03 (app quintet, *J* = 7 Hz, 1 H), 4.89 (app dt, *J* = 4, 10.5 Hz, 1 H), 6.42 (d, *J* = 7 Hz, 1 H), 7.13−7.16 (m, 1 H), 7.22−7.29 (m, 4 H), 7.45−7.48 (m, 2 H), 7.51−7.54 (m, 1 H), 7.76−7.78 (m, 2 H); MS (methane − CI) 448 (0.2, M + 41), 436 (0.4, M + 29), 408 [3, (M + H)$^+$], 194 (100), 176 (9.2), 105 (31.7). Anal. Calcd for $C_{26}H_{33}NO_3$: C, 76.63; H, 8.16; N, 3.44. Found: C, 76.89; H, 8.42; N, 3.53.

Determination of α-Stereochemistry. From **3a** (75.0 mg, 184 μmol), following general procedure D, was obtained *N*-benzoyl-(*S*)-alanine (27.2 mg, 77%) as a white solid: $[\alpha]_D$ +34.9° (*c* 1.0, $CHCl_3$), $[\alpha]_D$ +26.7° (*c* 1.0, 0.1 N NaOH) [lit.[30a] $[\alpha]_D$ = −35° (*c* 1.0, $CHCl_3$) for the (*R*)-isomer, lit.[30b] $[\alpha]^{21}_D$ = +26.7° (*c* 1.0, 0.1 N NaOH) for the (*S*)-isomer].

From **3b** (75.0 mg, 184 μmol), following general procedure D, was obtained *N*-benzoyl-(*R*)-alanine (25.4 mg, 72%) as a white solid: $[\alpha]_D$ −34.8° (*c* 1.0, $CHCl_3$), $[\alpha]_D$ −26.6° (*c* 1.0, 0.1 N NaOH) [lit.[30a] $[\alpha]_D$ = −35° (*c* 1.0, $CHCl_3$) for the (*R*)-isomer, lit.[30b] $[\alpha]^{21}_D$ = +26.7° (*c* 1.0, 0.1 N NaOH) for the (*S*)-isomer].

(1*R*,2*S*)-2-Phenylcyclohexyl *N*-Benzoyl-(*S*)-alaninate (2a)/(1*R*,2*S*)-2-Phenylcyclohexyl *N*-Benzoyl-(*R*)-alaninate (2b). From (1*R*,2*S*)-2-phenylcyclohexanol[31] (250 mg, 1.42 mmol) and *N*-benzoylalanyl chloride[16] (301 mg, 1.42 mmol), following general procedure A, was obtained **2** (476 mg, 95%), as a 1.1:1 mixture of diastereomers, epimeric at the α-carbon. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, *J* = 7, 3 H), 1.25−1.97 (m, 7 H), 2.13−2.15 (m, 1 H), 2.67−2.73 (m, 1 H), 4.51−4.63 (app quintet, *J* = 7 Hz, 1 H), 5.04−5.09 (app dt, *J* = 4, 11 Hz, 1 H), 6.54 (d, *J* = 6 Hz, 1 H), 7.12−7.27 (m, 5 H), 7.38−7.50 (m, 3 H), 7.69−7.71 (m, 2 H). Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25−1.97 (m, 7 H), 1.28 (d, *J* = 7, 3 H), 2.13−2.15 (m, 1 H), 2.67−2.73 (m, 1 H), 4.45−4.53 (app quintet, *J* = 7 Hz, 1 H), 5.00−5.05 (app dt, *J* = 4, 11 Hz, 1 H), 6.43 (d, *J* = 6 Hz, 1 H), 7.12−7.27 (m, 5 H), 7.38−7.50 (m, 3 H), 7.69−7.71 (m, 2 H); MS (**2a/2b**; methane − CI) 392 (1, M + 41), 380 (2, M + 29), 352 [21, (M + H)$^+$], 194 (100), 159 (56), 105 (18). Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found (**2a/2b**): C, 75.46; H, 7.11; N, 4.10.

(1*R*,2*R*,3*R*,5*S*)-2-Isopinocampheyl *N*-Benzoyl-(*S*)-alaninate (1a)/(1*R*,2*R*,3*R*,5*S*)-2-Isopinocampheyl *N*-Benzoyl-(*R*)-alaninate (1b). From (1*R*,2*R*,3*R*,5*S*)-isopinocampheol (250 mg, 1.62 mmol) and *N*-benzoylalanyl chloride[16] (377 mg, 1.78 mmol), following general procedure A, was obtained **1** (528 mg, 99%) as mixture (1:1) of diastereomers. *Listed NMR peaks are common to both diastereomers, unless otherwise stated*: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.95 (s, 3 H), 1.04 (d, *J* = 3 Hz, 1 H; from one diastereomer), 1.07 (d, *J* = 3 Hz, 1 H; from other diastiomer), 1.11 (d, *J* = 7 Hz, 3 H), 1.22 (s, 3 H), 1.51 (d, *J* = 7 Hz, 3 H; from one diastereomer), 1.52 (d, *J* = 7 Hz, 3 H; from other diastereomer), 1.63−1.69 (ddd, *J* = 3, 4, 14 Hz, 1 H; from one diastereomer), 1.71−1.77 (ddd, *J* = 3, 4, 14 Hz, 1 H; from other diastereomer), 1.80−1.85 (m, 1 H), 1.91−1.96 (m, 1 H), 2.09−2.18 (m, 1 H), 2.33−2.41 (m, 1 H), 2.54−2.63 (m, 1 H), 4.72−4.79 (dq, *J* = 5, 7 Hz, 1 H; from one diastereomer), 4.74−4.81 (dq, *J* = 5, 7 Hz, 1 H; from other diastereomer), 5.08−5.13 (app quintet, *J* = 5 Hz, 1 H; from one diastereomer), 5.09−5.14 (app quintet, *J* = 5 Hz, 1 H; from other diastereomer), 6.81 (broad s, 1 H), 7.40−7.48 (m, 2 H), 7.49-7.52 (m, 1 H), 7.78−7.81 (m, 1 H). Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found (**1a/1b**): C, 72.96; H, 8.23; N, 4.36.

General Procedure B. (1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-(*S*)-α-methylphenylalaninate (9). To a solution of diisopropylamine (120 μL, 0.797 mmol) and HMPA (1.6 mL) in THF (8 mL) at −78 °C was added *n*-butyllithium (0.62 mL, 1.28 M in *n*-hexane), and the resulting solution was stirred for 30 min at 0 °C and then cooled to −78 °C. Then, **3a** (250 mg, 0.613 mmol) in THF (8 mL) at −78 °C was added via

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cannula, followed by *n*-butyllithium (1.15 mL, 1.3 M in *n*-hexane), and the resulting deep red solution stirred for 1 h at −78 °C. Benzyl bromide (115 mg, 0.675 mmol) in THF (1 mL) at −78 °C was then added via cannula. After being stirred at −78 °C for 45 min, the reaction mixture was poured into ether (30 mL) and NH_4Cl (aqueous, 30 mL). After further extraction with ether (3 × 20 mL), the combined organics were dried ($MgSO_4$), filtered, evaporated, and chromatographed (10% EtOAc/hexane) to give **9** (229 mg, 75%, 88% de) as a white solid. One recrystallization (50 mg) from ether provided an analytical sample of **9** (34 mg, 100% de): mp 149−151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88−2.19 (m, 8 H), 0.95 (d, J = 6 Hz, 3 H), 1.26 (s, 3 H), 1.32 (s, 3 H), 1.60 (s, 3 H), 3.29 (d, J = 14 Hz, 1 H), 3.35 (d, J = 14 Hz, 1 H), 4.97−5.02 (app dt, J = 4, 11 Hz, 1 H), 6.58 (s, 1 H), 7.16−7.35 (m, 10 H), 7.44−7.47 (m, 2 H), 7.53−7.56 (m, 1 H), 7.70−7.72 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 23.4, 25.8, 27.3, 28.2, 31.4, 34.5, 40.1, 40.3, 41.6, 49.9, 61.2, 77.8, 125.4, 125.6, 126.7, 126.9, 128.1, 128.2, 128.5, 130.5, 131.4, 135.2, 136.6, 151.0, 166.9, 173.3. Anal. Calcd for $C_{33}H_{39}NO_3$: C, 79.64; H, 7.90; N, 2.81. Found: C, 79.61; H, 7.83; N, 2.82.

(1*R*,2*R*,3*R*,5*S*)-2-Isopinocampheyl *N*-Benzoyl-(*S*)-α-methylphenylalaninate (7a)/(1*R*,2*R*,3*R*,5*S*)-2-Isopinocampheyl *N*-Benzoyl-(*R*)-α-methylphenylalaninate (7b). From **1a/1b** (30.0 mg, 91 μmol) and benzyl bromide (16.0 mg, 91 μmol), following general procedure B, was obtained **7a/7b** (30.3 mg, 79%, 6% de) after flash chromatography (10% EtOAc/hexane). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 3 H), 1.05−1.09 (m, 1 H), 1.17 (d, J = 7 Hz, 3 H), 1.24 (s, 3 H), 1.65−1.67 (app t, J = 3.5 Hz, 1 H), 1.81 (s, 3 H), 1.83−1.87 (m, 1 H), 1.93−1.98 (m, 1 H), 2.26−2.29 (m, 1 H), 2.37−2.42 (m, 1 H), 2.57−2.63 (m, 1 H), 3.33 (d, J = 14 Hz, 1 H), 3.76 (d, J = 14 Hz, 1 H), 5.10−5.14 (app quintet, J = 4.5 Hz, 1 H), 6.89 (s, 1 H), 7.11−7.13 (m, 2 H), 7.18−7.20 (m, 3 H), 7.38−7.41 (m, 2 H), 7.46−7.49 (m, 1 H), 7.67−7.68 (m, 2 H). Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (s, 3 H), 1.05−1.09 (m, 1 H), 1.12 (d, J = 7 Hz, 3 H), 1.24 (s, 3 H), 1.68−1.70 (app t, J = 3.5 Hz, 1 H), 1.79 (s, 3 H), 1.83−1.87 (m, 1 H), 1.93−1.98 (m, 1 H), 2.10−2.13 (m, 1 H), 2.37−2.42 (m, 1 H), 2.57−2.63 (m, 1 H), 3.30 (d, J = 14 Hz, 1 H), 3.72 (d, J = 14 Hz, 1 H), 5.10−5.14 (app quintet, J = 4.5 Hz, 1 H), 6.84 (s, 1 H), 7.11−7.13 (m, 2 H), 7.18−7.20 (m, 3 H), 7.38−7.41 (m, 2 H), 7.46−7.49 (m, 1 H), 7.67−7.68 (m, 1 H). Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93; N, 3.34. Found (**7a/7b**): C, 77.16; H, 8.12; N, 3.36.

(1*R*,2*S*)-2-Phenylcyclohexyl *N*-Benzoyl-(*S*)-α-methylphenylalaninate (8a)/(1*R*,2*S*)-2-Phenylcyclohexyl *N*-Benzoyl-(*R*)-α-methylphenylalaninate (8b). From **2a/2b** (30 mg, 85 μmol) and benzyl bromide (16 mg, 94 μmol), following general procedure B, was obtained **8a/8b** (22 mg, 57%, 10% de) after SiO_2 chromatography (10% EtOAc/hexane). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87−2.25 (m, 8 H), 1.16 (s, 3 H), 2.75−2.80 (m, 1 H), 3.06 (d, J = 14 Hz, 1 H), 3.62 (d, J = 14 Hz, 1 H), 5.06−5.11 (app dt, J = 4, 11 Hz, 1 H), 6.40 (d, J = 8 Hz, 1 H), 6.75 (s, 1 H), 6.95−6.99 (m, 1 H), 7.01−7.08 (m, 1 H), 7.14−7.45 (m, 9 H), 7.47−7.49 (m, 1 H), 7.53−7.59 (m, 2 H). Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87−2.25 (m, 8 H), 1.57 (s, 3 H), 2.75−2.80 (m, 1 H), 2.95 (d, J = 14 Hz, 1 H), 3.45 (d, J = 14 Hz, 1 H), 4.96−5.01 (app dt, J = 4, 11 Hz, 1 H), 6.40 (d, J = 8 Hz, 1 H), 6.58 (s, 1 H), 6.95−6.99 (m, 1 H), 7.01−7.08 (m, 1 H), 7.14−7.45 (m, 9 H), 7.47−7.49 (m, 1 H), 7.53−7.59 (m, 2 H). Anal. Calcd for $C_{29}H_{31}NO_3$: C, 78.88; H, 7.07; N, 3.17. Found (**8a/8b**): C, 78.84; H, 7.32; N, 3.08.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-(*S*)-α-methylisovalinate (10).[24] From **3a** (250 mg, 0.613 mmol) and iodoethane (105 mg, 0.675 mmol), following general procedure B, was obtained **10** (180 mg, 68%, 86% de), after SiO_2 chromatography (10% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75−1.62 (m, 6 H), 0.81 (t, J = 7 Hz, 3 H), 0.89 (d, J = 6 Hz, 3 H), 1.27 (s, 3 H), 1.38 (s, 3 H), 1.56 (s, 3 H), 1.75−1.83 (m, 1 H), 2.00−2.09 (m, 2 H), 2.36−2.43 (m, 1 H), 4.96−5.01 (app dt, J = 4, 10.5 Hz, 1 H), 7.02 (s, 1 H), 7.14−7.17 (m, 1 H), 7.25−7.31 (m, 4 H), 7.43−7.52 (m, 3 H), 7.74−7.80 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.4, 21.7, 22.1, 25.4, 27.2, 28.9, 29.1, 31.4, 34.4, 40.2, 41.6, 49.9, 61.4, 77.3, 125.4, 125.6, 126.9, 128.1, 128.5, 131.3, 135.2, 150.6, 166.2, 174.3; MS (methane − CI) 436 [1, $(M + H)^+$], 222 (100), 176 (20), 105 (57). Anal. Calcd for $C_{28}H_{37}NO_3$: C, 77.20; H, 8.56; N, 3.22. Found: C, 77.10; H, 8.68; N, 3.22.

***N*-Benzoyl-(*S*)-α-methylaspartic Acid α-(1*R*,2*S*,5*R*)-8-Phenylmenthyl, β-*tert*-Butyl Ester (11).** From **3a** (250 mg, 0.613 mmol) and *tert*-butyl bromoacetate (132 mg, 0.675 mmol), following general procedure B, was obtained **11** (276 mg, 86%, 82% de), after flash chromatography (10% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78−1.59 (m, 6 H), 0.85 (d, J = 6 Hz, 3 H), 1.25 (s, 3 H), 1.35 (s, 3 H), 1.37 (s, 9 H), 1.50 (s, 3 H), 2.03−2.13 (m, 2 H), 2.63 (d, J = 17 Hz, 1 H), 3.33 (d, J = 17 Hz, 1 H), 4.96−5.01 (app dt, J = 4, 10.5 Hz, 1 H), 7.13−7.16 (m, 1 H), 7.25−7.31 (m, 4 H), 7.39−7.48 (m, 4 H), 7.75−7.77 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 22.3, 25.9, 27.2, 28.0, 28.3, 31.3, 34.5, 40.1, 40.9, 41.2, 49.8, 58.1, 77.6, 81.1, 125.4, 125.6, 126.9, 128.1, 128.5, 131.3, 135.0, 150.9, 166.4, 169.9, 173.2. Anal. Calcd for $C_{32}H_{43}NO_5$: C, 73.67; H, 8.31; N, 2.69. Found: C, 73.55 H, 8.59; N, 2.59.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-*O*-benzyl-(*S*)-α-methylserinate (12).[24] From **3a** (250 mg, 0.613 mmol) and benzyloxymethyl bromide (136 mg, 0.675 mmol), following general procedure B, was obtained **12** (214 mg, 66%, 78% de), after flash chromatography (10% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75−1.54 (m, 6 H), 0.80 (d, J = 6 Hz, 3 H), 1.21 (s, 3 H), 1.31 (s, 3 H), 1.44 (s, 3 H), 1.97−2.02 (m, 2 H), 3.65 (d, J = 9 Hz, 1 H), 4.03 (d, J = 9 Hz, 1 H), 4.43 (d, J = 12 Hz, 1 H), 4.49 (d, J = 12 Hz, 1 H), 4.93−4.98 (app dt, J = 4, 11 Hz, 1 H), 7.09−7.18 (m, 1 H), 7.21−7.28 (m, 10 H), 7.40−7.43 (m, 2 H), 7.47−7.50 (m, 1 H), 7.71−7.75 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 21.6, 25.4, 27.1, 28.5, 31.3, 34.4, 40.1, 41.3, 49.9, 61.3, 72.1, 73.4, 77.6, 125.4, 125.5, 126.9, 127.0, 127.6, 128.1, 128.3, 128.5, 131.5, 134.9, 137.8, 150.7, 167.1, 172.6. Anal. Calcd for $C_{34}H_{41}NO_4$: C, 77.39; H, 7.83; N, 2.65. Found: C, 77.12; H, 7.67; N, 2.64.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-(*S*)-α-methylcinnamylglycinate (13).[24] From **3a** (30 mg, 74 μmol) and *trans*-cinnamyl bromide (16 mg, 81 μmol), following general procedure B, was obtained **13** (26 mg, 66%, 88% de), after chromatography (10% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78−1.60 (m, 6 H), 0.79 (d, J = 6 Hz, 3 H), 1.24 (s, 3 H), 1.35 (s, 3 H), 1.57 (s, 3 H), 1.98−2.01 (m, 1 H), 2.04−2.10 (m, 1 H), 2.64−2.68 (dd, J = 7, 14 Hz, 1 H), 3.19−3.24 (dd, J = 7, 14 Hz, 1 H), 4.94−5.01 (app dt, J = 4, 10.5 Hz, 1 H), 5.99−6.04 (app quintet, J = 8 Hz, 1 H), 6.99 (s, 1 H), 7.12−7.21 (m, 2 H), 7.23−7.35 (m, 8 H), 7.38−7.41 (m, 2 H), 7.45−7.48 (m, 1 H), 7.73−7.75 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 22.3, 25.5, 27.2, 28.7, 31.4, 34.4, 39.4, 40.1, 42.0, 49.9, 60.8, 77.6, 123.8, 125.4, 125.6, 126.2, 126.9, 127.4, 128.1, 128.4, 128.5, 131.4, 134.2, 135.2, 137.0, 150.7, 166.5, 173.7; MS (EI) 523 (0.14, M^+), 402 (8), 188 (78), 105 (100); HRMS (EI) calcd for $C_{35}H_{41}NO_3$ 523.3086, obsd 523.3069.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-(*S*)-α-methylpropargylglycinate (14).[24] From **3a** (30 mg, 74 μmol) and propargyl bromide (9.6 mg, 81 μmol), following general procedure B, was obtained **14** (22 mg, 67%, 86% de), after SiO_2 chromatography (10% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81−1.61 (m, 6 H), 0.89 (d, J = 6 Hz, 3 H), 1.25 (s, 3 H), 1.34 (s, 3 H), 1.51 (s, 3 H), 1.96 (app t, J = 2 Hz, 1 H), 2.05−2.15 (m, 2 H), 2.73−2.77 (dd, J = 2, 17 Hz, 1 H), 2.99−3.03 (dd, J = 2, 17 Hz, 1 H), 4.95−5.00 (app dt, J = 4, 10.5 Hz, 1 H), 6.96 (s, 1 H), 7.15−7.18 (m, 1 H), 7.26−7.32 (m, 4 H), 7.42−7.45 (m, 2 H), 7.49−7.53 (m, 1 H), 7.77−7.79 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 22.0, 26.1, 26.2, 27.2, 27.9, 31.4, 34.5, 40.0, 41.3, 49.8, 59.3, 71.1, 77.8, 79.6, 125.4, 125.5, 127.0, 127.1, 128.2, 128.5, 131.5, 150.9, 166.7, 172.6; MS (EI) 445 (2, M^+), 406 (2, $-C_3H_3$), 232 (71), 186 (36); HRMS (EI) calcd for $C_{29}H_{35}NO_3$ 445.2617, obsd 445.2612.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-(*S*)-α-methylallylglycinate (15).[24] From **3a** (30.0 mg, 74 μmol) and allyl bromide (9.8 mg, 81 μmol), following general procedure B, was obtained **15** (23 mg, 69%, 88% de), after flash chromatography (10% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80−1.60 (m, 6 H), 0.87 (d, J = 6 Hz, 3 H), 1.25 (s, 3 H), 1.36 (s, 3 H), 1.54 (s, 3 H), 1.99−2.09 (m, 2 H), 2.49−2.53 (dd, J = 7, 14 Hz, 1 H), 2.96−3.00 (dd, J = 7, 14 Hz, 1 H), 4.93−4.98 (app dt, J

= 4, 10.5 Hz, 1 H), 5.08–5.09 (d, J = 8 Hz, 1 H), 5.09–5.12 (d, J = 15 Hz, 1 H), 5.59–5.66 (m, 1 H), 6.87 (s, 1 H), 7.12–7.15 (m, 1 H), 7.23–7.31 (m, 4 H), 7.40–7.43 (m, 2 H), 7.47–7.50 (m, 1 H), 7.73–7.75 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 22.2, 25.6, 27.2, 28.6, 31.4, 34.4, 40.1, 40.3, 41.7, 49.9, 60.1, 77.4, 119.4, 125.4, 125.6, 126.8, 128.1, 128.5, 131.3, 132.3, 135.2, 150.8, 166.4, 173.7. Anal. Calcd for $C_{29}H_{37}NO_3$: C, 77.82; H, 8.33; N, 3.13. Found: C, 77.61; H, 8.46; N, 3.00.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-(*S*)-α-methylleucinate (16). From **3a** (200 mg, 0.491 mmol) and isobutyl iodide (99.3 mg, 0.540 mmol), following general procedure B, was obtained **16** (196 mg, 86%, 78% de), after SiO_2 chromatography (10% EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75–1.71 (m, 8 H), 0.85–0.95 (m, 9 H), 1.25 (s, 3 H), 1.37 (s, 3 H), 1.55 (s, 3 H), 2.03–2.15 (m, 2 H), 2.28–2.35 (dd, J = 6, 14 Hz, 1 H), 4.93–5.01 (app dt, J = 4, 10.5 Hz, 1 H), 7.10–7.20 (m, 2 H), 7.22–7.33 (m, 4 H), 7.38–7.51 (m, 3 H), 7.73–7.79 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 23.4, 24.0, 25.1, 25.4, 27.3, 28.8, 31.4, 34.4, 40.1, 41.5, 43.8, 49.8, 60.8, 77.7, 125.4, 125.5, 126.8, 128.1, 128.5, 131.3, 135.3, 150.6, 166.2, 175.0. Anal. Calcd for $C_{30}H_{41}NO_3$: C, 77.71; H, 8.91; N, 3.02. Found: C, 77.86; H, 8.73; N, 2.86.

3,4-Bis((*tert*-butyldimethylsilyl)oxy)toluene (17). To a solution of 3-methylcatechol (1.0 g, 8.1 mmol), 4-(dimethylamino)pyridine (98 mg, 81 μmol), and imidazole (2.2 g, 32 mmol) in DMF (50 mL) was added *tert*-butyldimethylsilyl chloride (3.04 g, 20.1 mmol). The resulting reaction mixture was heated at 50 °C for 4 h and then poured into $NaHCO_3$ (aqueous, 75 mL) and Et_2O (50 mL). The aqueous layer was further extracted with Et_2O (2 × 50 mL), and the combined extracts were dried ($MgSO_4$) and evaporated. Chromatrography (20% EtOAc/hexane) provided **17** (2.82 g, 99%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 0.19 (s, 6 H), 0.97 (s, 9 H), 0.98 (s, 9 H), 2.21 (s, 3 H), 6.58–6.71 (m, 3 H); MS (methane – CI) 381 (6, M + 29), 353 [30, (M + H)$^+$], 337 (47), 295 (100), 115 (40). Anal. Calcd for $C_{19}H_{36}O_2Si_2$: C, 64.71; H, 10.29. Found: C, 64.72; H, 10.08.

3,4-Bis((*tert*-butyldimethylsilyl)oxy)benzyl Bromide (18). To a solution of **17** (1.50 g, 4.26 mmol), *N*-bromosuccinimide (835 mg, 4.69 mmol), and K_2CO_3 (60 mg, 43 μmol) in CCl_4 (9 mL) was added benzoyl peroxide (103 mg, 0.426 mmol). The resulting reaction mixture was heated to reflux for 12 h and then cooled to 0 °C. Hexane (20 mL) was added and the mixture filtered. The filtrate was washed with $NaHCO_3$ (aqueous, 5 mL) and H_2O (2 × 5 mL). The organic layer was dried ($MgSO_4$) and evaporated to afford **18** (1.74 g, 95%) as a pale yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 0.19 (s, 6 H), 0.97 (s, 9 H), 0.98 (s, 9 H), 4.42 (s, 2 H), 6.73–6.76 (m, 1 H), 6.81–6.86 (m, 2 H); MS (EI) 432 (1.5, M$^+$ for ^{81}Br), 430 (1.5, M$^+$ for ^{79}Br), 375 (3.5), 373 (3.3), 351 (13), 73 (100); HRMS (EI) calcd for $C_{19}H_{35}O_2Si_2Br$ (^{79}Br) 430.1343, obsd 430.1343.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl *N*-Benzoyl-3′-bis((*tert*-butyldimethylsilyl)oxy)-(*S*)-α-methylphenylalaninate (19).[24] From **3a** (300 mg, 0.736 mmol) and **18** (349 mg, 0.810 mmol), following general procedure B, was obtained **19** (402 mg, 72%, 88% de), after flash chromatography (10% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.15 (s, 3 H), 0.16 (s, 3 H), 0.85–1.62 (m, 6 H), 0.89 (d, J = 6 Hz, 3 H), 0.91 (s, 9 H), 0.95 (s, 9 H), 1.23 (s, 3 H), 1.32 (s, 3 H), 1.49 (s, 3 H), 1.99–2.14 (m, 2 H), 3.06 (d, J = 14 Hz, 1 H), 3.10 (d, J = 14 Hz, 1 H), 4.90–4.95 (app dt, J = 4, 11 Hz, 1 H), 6.49 (s, 1 H), 5.64–6.57 (m, 1 H), 6.59 (s, 1 H), 6.67 (d, J = 8 Hz, 1 H), 7.13–7.16 (m, 1 H), 7.23–7.31 (m, 4 H), 7.36–7.41 (m, 2 H), 7.45–7.49 (m, 1 H), 7.64–7.66 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.24, −4.18, −4.14, −4.03, 18.3, 18.4, 21.3, 23.1, 25.8, 25.9, 27.3, 28.1, 31.3, 31.4, 34.5, 39.9, 40.0, 41.4, 49.9, 60.7, 77.5, 120.3, 120.4, 123.3, 123.5, 125.2, 125.3, 125.5, 127.0, 128.1, 128.2, 128.4, 128.7, 129.5, 131.3, 135.0, 145.8, 146.3, 151.1, 166.6, 173.4; HRMS (FAB, 3-NOBA, LiI) calcd for $C_{45}H_{67}NO_5Si_2Li$ [(M + Li)$^+$] 764.4718, obsd 764.4718.

General Procedure C. (*S*)-α-Methylphenylalanine (20). A suspension of **9** (110 mg, 211 μmol) in 9 N HCl (2.2 mL) was heated at 120 °C in a sealed vessel for 7 h. The crude reaction mixture was extracted with CH_2Cl_2 (30 mL) and the aqueous layer evaporated in vacuo. The residue was applied to a Dowex 50 × 8 ion exchange column. After washing with several column volumes of H_2O, elution with 10% NH_4OH afforded **20** (20.9 mg, 53%) as a white solid: $[\alpha]_D$ (88% ee) −18.9° (c = 1.0, H_2O) [lit.[32] $[\alpha]_D$ −21.5° (c 1, H_2O)].

(*S*)-α-Methylaspartate (21). From **11** (150 mg, 287 μmol) in 9 N HCl (2.8 mL), following general procedure C, was obtained **21** (24.2 mg, 58%) as a white solid: $[\alpha]_D$ (82% ee) +43.1° (c 1.2, H_2O) [lit.[6g] $[\alpha]_D$ +52.8° (c 0.60, H_2O)].

(*S*)-α-Methylleucine (22). From **12** (150 mg, 323 μmol) in 9 N HCl (3.2 mL), following general procedure C, was obtained **22** (20.2 mg, 43%) as a white solid: $[\alpha]_D$ (78% ee) +26.1° (c 1.0, H_2O) [lit.[33] $[\alpha]_D$ +34.2° (c 3, H_2O)].

General Procedure D. *N*-Benzoyl-(*S*)-α-methylphenylalanine (23). To a solution of **9** (30.0 mg, 60.3 μmol) and 18-crown-6 (16.0 mg, 60.3 μmol) in benzene (2 mL) was added KO_2 (26.0 mg, 362 μmol), and the mixture was stirred at 50 °C for 4 d. The resulting mixture was partitioned between K_2CO_3 (aqueous, 5 mL) and Et_2O (10 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to give (−)-8-phenylmenthol[25] (14 mg, 76%). The aqueous layer was acidified to pH 2 with 10% $KHSO_4$ and then extracted with Et_2O. The extract was dried ($MgSO_4$), filtered, evaporated, and chromatographed (1:1:0.1 EtOAc/hexane/acetic acid) to give **23** (12.4 mg, 73%): ^{1}H NMR (300 MHz, DMSO) δ 1.32 (s, 3 H), 3.03 (d, J = 13 Hz, 1 H), 3.48 (d, J = 13 Hz, 1 H), 7.07–7.09 (m, 2 H), 7.19–7.26 (m, 3 H), 7.42–7.55 (m, 3 H), 7.76–7.79 (m, 2 H), 8.16 (s, 1 H), 12.44 (s, 1 H); MS (EI) 283 (1.6, M$^+$), 192 (22), 105 (100), 91 (13); HRMS (EI) calcd for $C_{17}H_{17}NO_3$ 283.1208, obsd 283.1202.

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Supplementary Material Available: ^{1}H NMR spectra for compounds **13**, **14**, **18**, **19**, and **23**, as well as of **9**, both before and after recrystallization (7 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.

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