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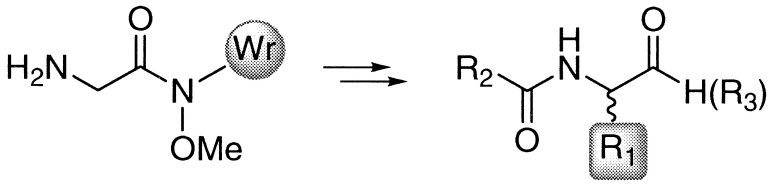

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UPS on Weinreb Resin: A Facile Solid-Phase Route to Aldehyde and Ketone Derivatives of "Unnatural" Amino Acids and Peptides

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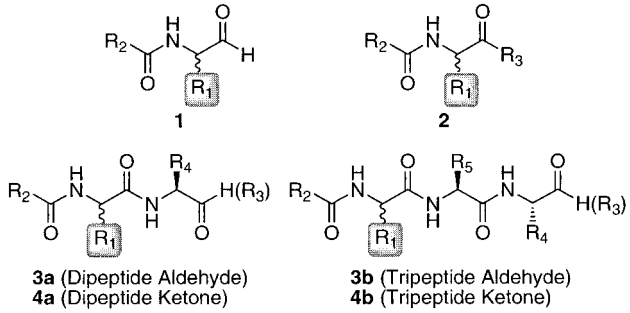
The solid-phase synthesis of "unnatural" amino aldehydes, amino ketones, peptide aldehydes, and peptide ketones was accomplished from commercially available resin in a series of room temperature reactions. The initial step involved addition of an "unnatural" side chain to the N-terminus of a benzophenone imine-activated Weinreb resin-bound amino acid or peptide derivative. The alkylated imine was hydrolyzed, and the amine was converted to the Boc-, Cbz-, or naphthoyl derivative. The resin-bound substrate was then cleaved with DIBAL-H or a Grignard reagent to give the amino aldehyde, amino ketone, peptide aldehyde, or peptide ketone products. Twenty-four reactions were carried out simultaneously using a "Billboard" reaction apparatus to give products in 27−87% (59% average) isolated yield.

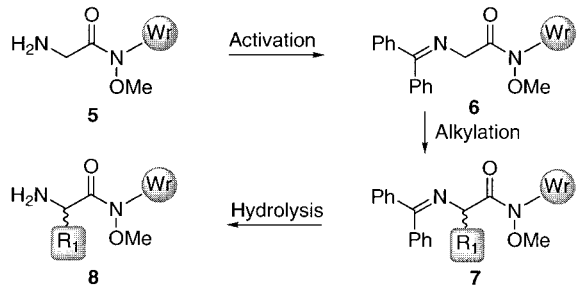
Naturally occurring amino acids are key biochemical building blocks and are useful starting materials for the preparation of a variety of compounds.[1] For example, amino aldehydes **1** and ketones **2**, as well as the corresponding peptide aldehydes **3** and ketones **4**, are prepared from amino acid derivatives (Scheme 1).[2,3]

Scheme 1. Amino Aldehydes (**1**) and Ketones (**2**) and Peptide Aldehydes (**3**) and Ketones (**4**)



These products have found utility as enzyme inhibitors, probes of peptide structure−function relationships, and as precursors for the preparation of other compounds. Weinreb amide derivatives of amino acids or peptides[4,5] are particularly valuable in the preparation of these compounds, via their reaction with hydride (to the aldehyde) or a carbanion (to the ketone).[6−11] The scope of products available through this chemistry is limited by the availability of either the natural or separately synthesized "unnatural" amino acid precursors. Our own recent solid-phase approach to unnatural amino acid and peptide synthesis (termed "UPS") provides a convenient, room temperature route for attachment of various types of substituents directly onto a resin-bound amino acid or peptide.[12−14] In this paper, we extend this chemistry to the preparation of amino aldehydes and ketones, as well as peptide aldehydes and ketones, by combining UPS and Weinreb methodologies. This methodology provides ready access, via solid-phase combinatorial techniques, to a broad range of structurally diverse "unnatural" amino acid- or peptide-derived products **1**−**4**. In addition to the normal diversity available at the sites shown, R_1 can now equal an "unnatural" side chain introduced during the solid-phase synthetic sequence.

Scheme 2. UPS Alkylation Sequence on Weinreb Resin-Bound Substrate



The critical sequence to the alkylated solid-phase Weinreb intermediates involves activation of the Weinreb resin-bound glycine **5** via the benzophenone imine to form **6**, alkylation (base and alkyl halide) to the alkylated derivative **7**, followed by selective hydrolysis of the imine to yield the Weinreb resin-bound alkylated amino amide derivative **8** (Scheme 2).

Initial studies were carried out in solution in order to determine the appropriate base for deprotonation of the

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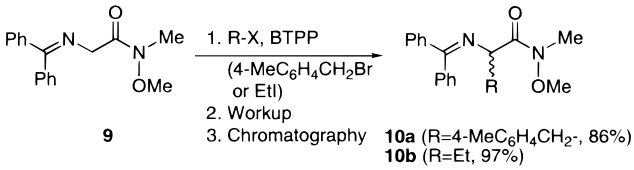
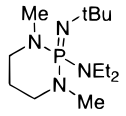
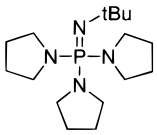
Scheme 3. Solution-Phase Studies for UPS Alkylation of Weinreb Amide Substrates



benzophenone imine Weinreb amide of glycine (**9**) (Scheme 3). Starting material **9** was prepared in three steps from Boc-Gly-OH in 54% overall yield. Alkylation of **9** proved sluggish with the normal UPS "base of choice," the organic soluble, nonionic Schwesinger base, BEMP.[12,15,16] By changing to the slightly stronger Schwesinger base, BTPP,[15,16] the alkylation of **9** was smoothly accomplished to give products **10**.

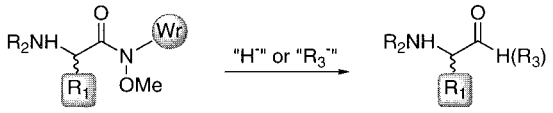




Using the methodology developed in solution, the synthesis of amino acid and peptide aldehydes and ketones was then effected in a solid-phase combinatorial manner. The resin-bound Schiff base glycine amide **6** was prepared by standard methodology in four steps from the commercially available Fmoc-Weinreb-AM resin. It is noteworthy that Schiff base amide **6** can conveniently be prepared from either Fmoc- or Boc-protected amino acids due to the known stability of the resin to mild acid or base.

Alkylation of the resin-bound, activated glycine amide **6** was followed by imine hydrolysis and then conversion to either Boc-, Cbz-, or naphthoyl derivatives. The naphthoyl derivatives led to UV active products, which simplified HPLC analysis. Cleavage from the resin was accomplished with DIBAL-H or Grignard reagents (Scheme 4). The

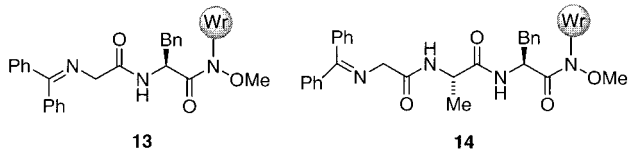
Scheme 4. Organometallic Cleavage of Weinreb Resin-Bound Intermediate To Yield Amino Aldehyde or Ketone Product



tetrahedral intermediate resulting from treatment with the organometallic reagent was quenched with 1 N HCl solution, the reaction mixture was filtered, and the filtrate was dried in vacuo. The inorganic salts were removed by redissolving the product in ethyl acetate and filtering through a short column of silica gel.

The utility and breadth of product diversity from this methodology was demonstrated by the *simultaneous* synthesis of twenty-four compounds (**12a**−**12p**, Chart 1 and **15a**−**15h**, Chart 2). With the single exception of the attempted preparation of *tert*-butyl ketones (**12m** and **12n**), which was not successful, the purity of the crude products was good to excellent (56−95% range of purities, 76% average purity). Furthermore, all crude products were subjected to flash chromatography to give pure product samples, which were characterized by NMR and high-resolution mass spectra. The UPS alkylation step was limited to two general cases. The representative active alkyl halide, 4-methylbenzyl bromide, was chosen because the aromatic methyl group serves as a good NMR marker. Ethyl iodide was used as a typical unactivated primary halide.[12c] The reduction of the Weinreb amides to the corresponding aldehydes with DIBAL-H proved to be a cleaner reaction than with LAH, in agreement with reports by others.[5b] Similarly, Grignard reagents were better than the alkyllithiums for the preparation of ketone products.[17] In this way a wide array of structurally diverse products was produced (Chart 1). Dipeptide and tripeptide aldehydes and ketones (**15a**−**15h**, Chart 2) were also accessible by this methodology, starting from the activated Gly-Phe or Gly-Ala-Phe Weinreb amide resins (**13** and **14**) (Scheme 5). Since BTPP

Scheme 5. Di- and Tripeptide Starting Substrates Used To Prepare Products **15**



was used for the earlier alkylations α to the Weinreb link, its continued use in UPS alkylations remote from the C-terminal residue was examined. UPS alkylations at the N-terminus of **13** or **14**, followed by cleavage from the resin with either DIBAL-H or MeMgCl gave the di- and tripeptide aldehydes and methyl ketones as mixtures of epimers at the N-terminal α-carbon. However, because of the increased basicity of BTPP,[16] we were concerned that its use in UPS with peptides might result in epimerization of preexisting stereocenters.[18] To address this question in the general context of UPS alkylations, a study was conducted on Wang resin-bound peptides, using BTPP and, for comparison, the milder base, BEMP.[16] The effect of these bases on the stereochemical fate of L-Phe during the UPS alkylation of Gly-Ala-Phe-Wang resin was determined.[19] It was assumed that epimerization of the C-terminal L-Phe on the Wang resin would be a more sensitive probe since this residue should be more readily deprotonated by virtue of its proximity to an ester rather than an amide functionality.[20] Under conditions for alkylation with activated alkyl halides (2 equiv of base and 2 equiv of RX), no measurable epimerization was observed with either base, BEMP or BTPP. However, using alkylation conditions for unactivated halides (10 equiv of base and 10 equiv of alkyl halide), with the weaker base BEMP a small amount of epimerization was noted (increase of 2% D-Phe over the control). With the stronger base BTPP, even more epimerization was evident (increase of 6.5% D-Phe over the control).[19] These results indicate that caution must be used when alkylating non-C-terminal residues in peptides with BTPP. For such cases, BEMP is the base of choice.[21] As described earlier, C-terminal alkylations on the Weinreb

Chart 1. Structures and Isolated Yields of Amino Aldehydes and Ketones from UPS-Acylation-Weinreb Reactions of Substrate **6**

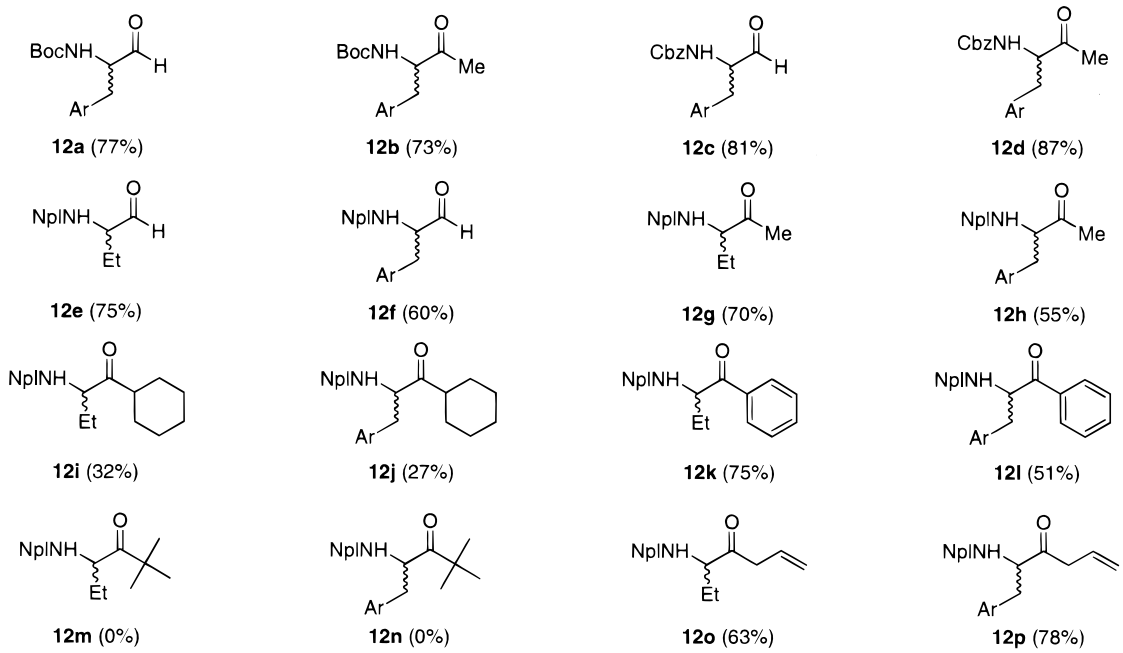
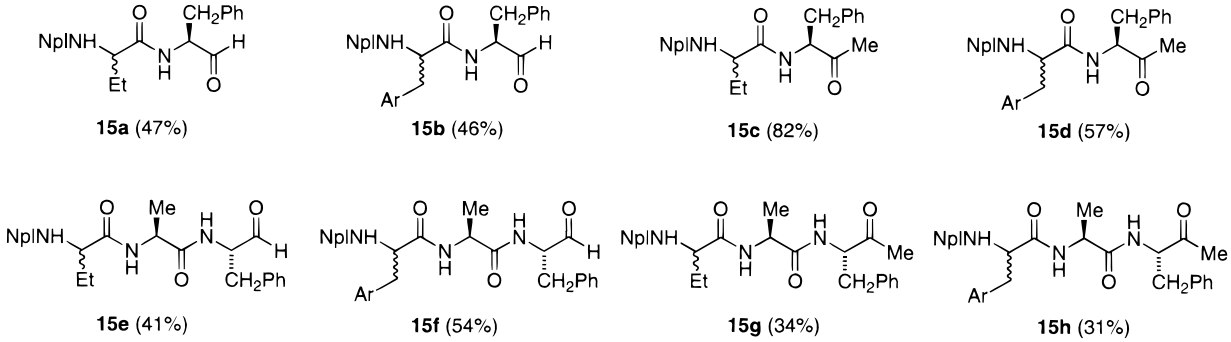


Chart 2. Structures and Isolated Yields of Peptide Aldehydes and Ketones from UPS-Acylation-Weinreb Reactions of Substrates **13** and **14**



resin should be conducted using BTPP as base because of the lower acidity of the proton on the α-carbon at this center.

This solid-phase synthesis of unnatural amino and peptide aldehydes and ketones should provide a valuable new synthetic tool. The room temperature reactions and the opportunity to introduce diversity at multiple sites in the final product provide a powerful method for producing large libraries of compounds in good to excellent yields and purities.

Experimental Section

General Methods. *N*-Boc-amino acids and Weinreb amide resin (Catalog No. 01-64-0153, Lots A18775 and A20071) were purchased from NovaBiochem. Anhydrous NMP and DMF, Boc-ON, Cbz-Cl, BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine), and BTPP (*tert*-butylimino-tri(pyrrolidino)phosphorane) were purchased from Aldrich or Fluka. DIBAL-H (1.0 M in dichloromethane), MeMgCl (3.0 M in THF), *c*-C_6H_{11}MgCl (2.0 M in diethyl ether), PhMgBr (3.0 M in diethyl ether), *t*-BuMgCl (1.0 M in THF), AllylMgCl (1.0 M in THF) were purchased from Aldrich. Isobutylchloroformate and *N*,*O*-dimethylhydroxylamine hydrochloride were purchased from Acros. THF was distilled from sodium benzophenone ketyl, and CH_2Cl_2 was distilled from CaH_2.

NMR analyses were performed using a GE QE 300 MHz NMR. Chemical shifts are given as δ in ppm relative to Me_4-Si as internal standard in $CDCl_3$ unless otherwise noted.

Electrospray ionization mass spectrometry was conducted using a PESciex API III triple stage quadrupole mass spectrometer operated in the positive ion detection mode. High-resolution mass spectrometry was run in the FAB mode.

General Procedures for Multiple Solid-Phase Reactions. The Billboard apparatus[22] was designed to simplify and expedite multiple manual solid-phase organic synthesis. Up to 24 reactions were performed simultaneously in fritted glass reaction vessels (RV) contained in a 6 × 9 in. Teflon or polypropylene board. The RVs were purchased from Kontes in the following approximate volumes: 3.5 mL (#34-5877), 6 mL (#34-5877-1), and 25 mL (#34-7805).

Typically, 50 μmol reactions were run in 3.5 mL RV, and up to 2 g of resin was used in the larger (25 mL) vessel for bulk synthesis. The appropriate amount of resin was weighed into the RV which was then inserted into the Billboard. A

small amount of grease on the O-ring of the RV was used to aid insertion.

General Washing. The resin was washed at least three times with each solvent. A squirt bottle, Pasteur pipet, automatic pipet, or other device was used. Any resin adhering to the cap liner was rinsed back into the RV by using a squirt bottle and holding the cap at an angle over the RV.

The volume of solvent for each wash was approximately 10−15 mL/g of resin. However, many times the resin or reagents adhered to the sides of the RV. In this case, the RV was filled completely with solvent. The solvent was allowed to drain by gravity for a few seconds and the remaining liquid was pushed through by positive Ar pressure. Use of an upside down 14/20 septum with a needle inserted worked well for this procedure. For larger RV, 24/40 septa were used. Flushing with Ar gas was used to introduce a "dry, inert" atmosphere when required.

Introduction of Reagents. Generally, reagents were introduced as 1 M stock solutions, and the reaction mixture was diluted as needed. Prior to addition of reagents, the bottom cap was placed on the RV, then solvents and reagents were added, and the top cap was placed on the RV (hand tightened only). Vigorous mixing by shaking the Billboard suspended the resin, and then the reaction vessels were mixed by gentle rotation using a rotary evaporator or mechanical stirrer. Reactions that build up pressure, such as the TFA deprotection of Boc derivatives, were vented occasionally by twisting the tops and then retightening.

Collection of Products. The products were collected into tared tool-neck vials by first inverting the Billboard, removing the bottom caps, and then placing the vials over the bottom of the RV. After all vials were in place, the collection rack was placed on top, and the whole apparatus was turned right side up. The top caps were loosened and then washed to remove any product. The resin was washed with the reaction solvent two to three times. This solution was concentrated by evaporation and then dried in vacuo to a residue.

2-[(Diphenylmethylene)amino]-*N*-methoxy-*N*-methylacetamide (9). To a stirred solution of Boc-Gly-OH (0.88 g, 5.0 mmol) and *N*-methylmorpholine (1.10 mL, 10 mmol) in dry CH_2Cl_2 (20 mL) at −15 °C was added isobutylchloroformate (0.65 mL, 5.0 mmol), and stirring was continued for 20 min at the same temperature. *N*,*O*-Dimethylhydroxylamine hydrochloride (0.49 g, 5.05 mmol) was added in one portion. After the mixture was stirred for 1 h, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature and then stirred overnight. The reaction mixture was poured into H_2O (20 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed in vacuo to give a white solid (1.01 g).

The white solid (1.0 g, 4.6 mmol) was dissolved in CH_2Cl_2 (10 mL), and TFA (5 mL) was added. The solution was stirred for 1.5 h at room temperature. The solvent and volatiles were removed in vacuo to give a viscous yellow oil.

The viscous oil from the previous step was dissolved in dry CH_2Cl_2 (15 mL), and benzophenone imine (1.01 mL, 6 mmol) was added. The solution was stirred for 24 h at room temperature. The reaction mixture was poured into H_2O (25 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo to give a viscous yellow oil. Flash chromatography (silica gel; hexane:ethyl acetate; 3:1; v/v) of the crude product gave pure **9** as a pale yellow oil (0.70 g, 54%). TLC R_f 0.18 (silica gel; hexane:ethyl acetate; 3:1; v/v); ^{1}H NMR ($CDCl_3$) δ 3.20 (s, 3H), 3.62 (s, 3H), 4.35 (s, 2H), 7.21−7.55 (m, 8H), 7.60−7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 31.9, 54.3, 60.9, 127.4, 127.5, 128.1, 128.2, 129.8, 135.7, 139.0, 170.9; HRMS *m*/*z* calcd for $C_{17}H_{18}N_2O_2$ 283.1447 for (M + H$^+$), found 283.1462.

α-[(Diphenylmethylene)amino]-*N*-methoxy-*N*,4-dimethylbenzenepropanamide (10a). To a magnetically stirred solution of the Schiff base amide **9** (0.125 g, 0.44 mmol) and 4-methylbenzyl bromide (0.16 g, 0.89 mmol) in dry THF (1 mL) was added BTPP (0.27 mL, 0.89 mmol). The solution was stirred overnight at room temperature. The reaction mixture was poured into H_2O (10 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to give an oil. Flash chromatography (silica gel; hexane:ethyl acetate; 1:1; v/v) of the crude product gave pure product **10a** as a colorless oil (0.15 g, 86%). TLC R_f 0.47 (silica gel; hexane:ethyl acetate; 1:1; v/v); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 2.97 (dd, J = 7.4, 13.2 Hz, 1H), 3.11 (s, 3H), 3.15 (s, 3H), 3.30 (dd, J = 5.9, 13.2 Hz, 1H), 4.56 (t, J = 6.6 Hz, 1H), 6.83−6.85 (m, 2H), 6.90 (d, J = 8.1 Hz, 2H), 6.98 (d, J = 8.1 Hz, 2H), 7.27−7.39 (m, 6H), 7.63−7.66 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 32.2, 29.3, 60.6, 64.8, 127.5, 127.7, 127.9, 128.0, 128.5, 128.6, 129.3, 129.9, 135.4, 136.5, 139.2, 169.5; HRMS *m*/*z* calcd for $C_{25}H_{26}N_2O_2$ 387.2072 for (M + H$^+$), found 387.2082.

2-[(Diphenylmethylene)amino]-*N*-methoxy-*N*-methylbutanamide (10b). The reaction was carried out in an identical manner as above using Schiff base amide **9** (0.073 g, 0.26 mmol), ethyl iodide (0.21 mL, 2.6 mmol), and BTPP (0.79 mL, 2.6 mmol) in dry THF (1.5 mL). Flash chromatography (silica gel; hexane:ethyl acetate; 1:1; v/v) of the crude product gave pure **10b** as a colorless oil (0.07 g, 97%). TLC R_f 0.40 (silica gel; hexane:ethyl acetate; 1:1; v/v); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 3H), 1.68−1.82 (m, 1H), 2.00−2.14 (m, 1H), 3.16 (s, 3H), 3.26 (s, 3H), 4.26 (dd, J = 5.9, 12.5 Hz, 1H), 7.17−7.48 (m, 8H), 7.65−7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 10.8, 26.9, 32.4, 60.7, 64.4, 127.8, 128.3, 128.7, 130.0, 136.9, 139.5, 169.3; HRMS *m*/*z* calcd for $C_{19}H_{22}N_2O_2$ 311.1759 for (M + H$^+$), found 311.1759.

Preparation of the Benzophenone Imine of Gly-Weinreb Resin (6). The Fmoc-Weinreb resin (2.20 g, 1.19 mmol) was weighed into a 25 mL capacity Billboard reaction vessel and was washed with CH_2Cl_2 (3 × 20 mL), DMF (3 × 20 mL), and 20% piperidine in DMF (2 × 20 mL). A solution of 20% piperidine in DMF (20 mL) was added, and the

reaction solution was mixed by rotating for 1 h. The piperidine/DMF solution was drained, and the resin was washed with DMF (3 × 20 mL) and NMP (3 × 20 mL).

Boc-Gly-OH (1.04 g, 5.94 mmol, 5 equiv), HOAt (0.81 g, 5.94 mmol, 5 equiv), and DIC (0.93 mL, 5.94 mmol, 5 equiv) in NMP were added to the resin. DIEA was added until the pH of the solution was approximately 8 (the solution turned bright yellow upon addition of DIEA), and the vessel was rotated for 24 h. The solution was drained and washed with NMP (3 × 20 mL), CH_2Cl_2:MeOH (1:1, v/v; 3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and TFA:CH_2Cl_2 (1:1, v/v; 2 × 20 mL). A solution of TFA:CH_2Cl_2 (1:1, v/v; 20 mL) was added, and the vessel was rotated for 4 h. (*CAUTION!* Vessel pressure increased during the reaction.) The solution was drained, and the resin was washed with CH_2Cl_2 (3 × 20 mL) and NMP (3 × 20 mL). Benzophenone imine (1.99 mL, 11.88 mmol, 10 equiv) in NMP (20 mL) was added, and the vessel was rotated for 24 h. The vessel was drained, and the resin was washed with NMP (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), THF (3 × 20 mL), THF:H_2O (3:1, v/v; 3 × 20 mL), THF (3 × 20 mL), and CH_2Cl_2 (3 × 20 mL). The resin was dried under reduced pressure (1 mmHg, 40 °C, 8 h) to afford the resin-bound Schiff base product with a theoretical loading of 0.54 mmol/g.

Preparation of the Benzophenone Imine of Gly-Phe-Weinreb Resin (13). The Fmoc-Weinreb resin (1.40 g, 0.76 mmol) was weighed into a 25 mL capacity Billboard reaction vessel and was washed with CH_2Cl_2 (3 × 20 mL), DMF (3 × 20 mL), and 20% piperidine in DMF (2 × 20 mL). A solution of 20% piperidine in DMF (20 mL) was added, and the reaction solution was mixed by rotating for 1 h. The piperidine/DMF solution was drained, and the resin was washed with DMF (3 × 20 mL) and NMP (3 × 20 mL).

Boc-Phe-OH (1.0 g, 3.78 mmol, 5 equiv), HOAt (0.52 g, 3.78 mmol, 5 equiv) and DIC (0.59 mL, 3.78 mmol, 5 equiv) in NMP were added to the resin. DIEA was added until the pH of the solution was approximately 8 (the solution turned bright yellow upon addition of DIEA), and the vessel was rotated for 24 h. The solution was drained and washed with NMP (3 × 20 mL), CH_2Cl_2:MeOH (1:1, v/v; 3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and TFA:CH_2Cl_2 (1:1, v/v; 2 × 20 mL). A solution of TFA:CH_2Cl_2 (1:1, v/v; 20 mL) was added, and the vessel was rotated for 2 h. (*CAUTION!* Vessel pressure increased during the reaction.) The solution was drained, and the resin was washed with CH_2Cl_2 (3 × 20 mL), NMP (3 × 20 mL), NMP:DIEA (9:1, v/v, 3 × 20 mL), NMP (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and NMP (3 × 20 mL). Boc-Gly-OH (0.66 g, 3.78 mmol, 5 equiv), HOBt (0.57 g, 3.78 mmol, 5 equiv), and DIC (0.59 mL, 3.78 mmol, 5 equiv) in NMP were added to the resin, and the vessel was rotated for 24 h. The solution was drained and washed with NMP (3 × 20 mL), CH_2Cl_2:MeOH (1:1, v/v; 3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and TFA:CH_2Cl_2 (1:1, v/v; 2 × 20 mL). A solution of TFA:CH_2Cl_2 (1:1, v/v; 20 mL) was added, and the vessel was rotated for 2 h. (*CAUTION!* Vessel pressure increased during the reaction.) The solution was drained, and the resin was washed with CH_2Cl_2 (3 × 20 mL) and NMP (3 × 20 mL). Benzophenone imine (1.27 mL, 7.56 mmol, 10 equiv) in NMP (20 mL) was added, and the vessel was rotated for 24 h. The vessel was drained, and the resin was washed with NMP (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), THF (3 × 20 mL), THF:H_2O (3:1, v/v; 3 × 20 mL), THF (3 × 20 mL), and CH_2Cl_2 (3 × 20 mL). The resin was dried under reduced pressure (1 mmHg, 40 °C, 8 h) to afford the resin-bound Schiff base product with a theoretical loading of 0.50 mmol/g.

Preparation of the Benzophenone Imine of Gly-Ala-Phe-Weinreb Resin (14). The Fmoc-Weinreb resin (1.50 g, 0.81 mmol) was weighed into a 25 mL capacity Billboard reaction vessel and was washed with CH_2Cl_2 (3 × 20 mL), DMF (3 × 20 mL), and 20% piperidine in DMF (2 × 20 mL). A solution of 20% piperidine in DMF (20 mL) was added, and the reaction solution was mixed by rotating for 1 h. The piperidine/DMF solution was drained, and the resin was washed with DMF (3 × 20 mL) and NMP (3 × 20 mL).

Boc-Phe-OH (1.07 g, 4.05 mmol, 5 equiv), HOAt (0.55 g, 4.05 mmol, 5 equiv), and DIC (0.64 mL, 4.05 mmol, 5 equiv) in NMP were added to the resin. DIEA was added until the pH of the solution was approximately 8 (the solution turned bright yellow upon addition of DIEA), and the vessel was rotated for 24 h. The solution was drained and washed with NMP (3 × 20 mL), CH_2Cl_2:MeOH (1:1, v/v; 3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and TFA:CH_2Cl_2 (1:1, v/v; 2 × 20 mL). A solution of TFA:CH_2Cl_2 (1:1, v/v; 20 mL) was added, and the vessel was rotated for 2 h. (*CAUTION!* Vessel pressure increased during the reaction.) The solution was drained, and the resin was washed with CH_2Cl_2 (3 × 20 mL), NMP (3 × 20 mL), NMP:DIEA (9:1, v/v, 3 × 20 mL), NMP (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and NMP (3 × 20 mL). Boc-Ala-OH (0.77 g, 4.05 mmol, 5 equiv), HOBt (0.55 g, 4.05 mmol, 5 equiv), and DIC (0.64 mL, 4.05 mmol, 5 equiv) in NMP were added to the resin, and the vessel was rotated for 24 h. The solution was drained and washed with NMP (3 × 20 mL), CH_2Cl_2:MeOH (1:1, v/v; 3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and TFA:CH_2Cl_2 (1:1, v/v; 2 × 20 mL). A solution of TFA:CH_2Cl_2 (1:1, v/v; 20 mL) was added, and the vessel was rotated for 2 h. (*CAUTION!* Vessel pressure increased during the reaction.) The solution was drained, and the resin was washed with CH_2Cl_2 (3 × 20 mL), NMP (3 × 20 mL), NMP:DIEA (9:1, v/v, 3 × 20 mL), NMP (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and NMP (3 × 20 mL). Boc-Gly-OH (0.71 g, 4.05 mmol, 5 equiv), HOBt (0.55 g, 4.05 mmol, 5 equiv), and DIC (0.64 mL, 4.05 mmol, 5 equiv) in NMP were added to the resin, and the vessel was rotated for 24 h. The solution was drained and washed with NMP (3 × 20 mL), CH_2Cl_2:MeOH (1:1, v/v; 3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and TFA:CH_2Cl_2 (1:1, v/v; 2 × 20 mL). A solution of TFA:CH_2Cl_2 (1:1, v/v; 20 mL) was added, and the vessel was rotated for 2 h. (*CAUTION!* Vessel pressure increased during the reaction.) The solution was drained, and the resin was washed with CH_2Cl_2 (3 × 20 mL) and NMP (3 × 20 mL). Benzophenone imine (1.36 mL, 8.10 mmol, 10 equiv) in NMP (20 mL) was added, and the vessel was rotated for 24 h. The vessel

was drained, and the resin was washed with NMP (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), THF (3 × 20 mL), THF:H_2O (3:1, v/v; 3 × 20 mL), THF (3 × 20 mL), and CH_2Cl_2 (3 × 20 mL). The resin was dried under reduced pressure (1 mmHg, 40 °C, 8 h) to afford the resin-bound Schiff base product with a theoretical loading of 0.48 mmol/g.

Alkylation of the Benzophenone Imine of Gly-X-Weinreb Resin (6 or 13 or 14) with an Activated Alkyl Halide. The benzophenone imine of Gly-Weinreb resin (50 μmol) was weighed into a 3.5 mL Billboard reaction vessel and was washed with CH_2Cl_2 (3 × 2.0 mL) and NMP (3 × 2.0 mL). 4-Methyl benzyl bromide (0.019 g, 100 μmol, 2 equiv) in NMP (1.5 mL) and then BTPP (0.03 mL, 100 μmol, 2 equiv) were added. The reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (3 × 2.0 mL), CH_2Cl_2 (3 × 2.0 mL), THF (3 × 2.0 mL), THF:H_2O (3:1, v/v; 3 × 2.0 mL), and THF (3 × 2.0 mL).

Alkylation of the Benzophenone Imine of Gly-X-Weinreb Resin (6 or 13 or 14) with an Unreactive Alkyl Halide. The benzophenone imine of Gly-Weinreb resin (50 μmol) was weighed into a 3.5 mL Billboard reaction vessel and was washed with CH_2Cl_2 (3 × 2.0 mL) and NMP (3 × 2.0 mL). Ethyl iodide (0.04 mL, 500 μmol, 10 equiv) in NMP (1.5 mL) and then BTPP (0.15 mL, 500 μmol, 10 equiv) were added. The reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (3 × 2.0 mL), CH_2Cl_2 (3 × 2.0 mL), THF (3 × 2.0 mL), THF:H_2O (3:1, v/v; 3 × 2.0 mL), and THF (3 × 2.0 mL).

Hydrolysis of the Imine in Resin-Bound Alkylated Products. The resin-bound imine (50 μmol) was washed with THF (3 × 2.0 mL) and THF:1 N HCl (2:1, v/v; 2 × 2.0 mL), THF:1 N HCl (2:1, v/v; 1.5 mL) was added, and the reaction mixture was rotated for 4 h. The resin was filtered and washed with NMP (3 × 2.0 mL), 10% DIEA/NMP (3 × 2.0 mL), NMP (3 × 2.0 mL), CH_2Cl_2 (3 × 2.0 mL), and NMP (3 × 2.0 mL).

Acylation of Resin-Bound Products with Boc. The resin-bound amine (50 μmol) was washed with DMF (3 × 2.0 mL). Boc-ON (0.123 g, 500 μmol, 10 equiv) in DMF (1.5 mL) was added, and the reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (3 × 2.0 mL), CH_2Cl_2 (3 × 2.0 mL), MeOH:CH_2Cl_2 (1:1, v/v; 3 × 2.0 mL), MeOH (3 × 2.0 mL), and CH_2Cl_2 (3 × 2.0 mL).

Acylation of Resin-Bound Products with Cbz. The resin-bound amine (50 μmol) was washed with DMF (3 × 2.0 mL). Benzyl chloroformate (0.71 mL, 500 μmol, 10 equiv) and DIEA (0.87 mL, 500 μmol, 10 equiv) in DMF (1.5 mL) were added, and the reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (3 × 2.0 mL), CH_2Cl_2 (3 × 2.0 mL), MeOH:CH_2Cl_2 (1:1, v/v; 3 × 2.0 mL), MeOH (3 × 2.0 mL), and CH_2Cl_2 (3 × 2.0 mL).

Acylation of Resin-Bound Products with Naphthoic Acid. The resin-bound amine (50 μmol) was washed with NMP (3 × 2.0 mL). 2-Naphthoic acid (0.086 g, 500 μmol, 10 equiv), HOBt (0.068 g, 500 μmol, 10 equiv), and DIC (0.078 mL, 500 μmol, 10 equiv) in NMP (1.5 mL) were added, and the reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (3 × 2.0 mL), CH_2Cl_2 (3 × 2.0 mL), MeOH:CH_2Cl_2 (1:1, v/v; 3 × 2.0 mL), MeOH (3 × 2.0 mL), and CH_2Cl_2 (3 × 2.0 mL).

Cleavage of Products from the Resin. The following reactions were carried out under an atmosphere of argon. The acylated Weinreb resin (50 μmol) was washed with freshly distilled, dry THF (3 × 2.0 mL). The reaction vessel bottom was capped. Freshly distilled, dry THF (1.0 mL) and the organometallic reagent (RMgX or DIBALH, 250 μmol, 5 equiv) were added, and the reaction mixture was rotated for 2 h. Next, 1 N HCl:THF (1:1, v/v, 0.5 mL) was carefully added to the vessel (*CAUTION!* effervescence), and the mixture was rotated for 15 min. The solution was drained into a vial, and the resin was washed with THF (2 × 2.0 mL) and CH_2Cl_2 (3 × 2.0 mL). The combined filtrates were evaporated to dryness, and the residue was dissolved in ethyl acetate (ca. 5.0 mL). The solution was passed through a Bond-Elut silica gel column (Varian 0010-2002) and was eluted with ethyl acetate (ca. 5.0 mL). The filtrate was evaporated to dryness, the crude product was subjected to flash chromatography using the indicated TLC solvent system, and the combined fractions were dried in vacuo (1 mmHg, 40 °C, 8 h) to give the product.

An alternative aqueous extractive workup could also be used. Following the 1 N HCl:THF hydrolysis and resin washes with THF and CH_2Cl_2, the combined filtrates were washed with water (1 × 6.0 mL), dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo to give the crude product, which was subjected to flash chromatography.

1,1-Dimethylethyl [1-formyl-2-(4-methylphenyl)ethyl]-carbamate (12a): yield (77%); TLC R_f 0.40 (silica gel; hexane:ethyl acetate; 2:1; v/v); ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.33 (s, 3H), 3.06 (d, J = 6.6 Hz, 2H), 4.40 (q, J = 5.9 Hz, 1H), 5.03 (br s, 1H), 7.08 (d, J = 7.4 Hz, 2H), 7.14 (d, J = 7.4 Hz, 2H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 29.3, 36.1, 55.4, 63.1, 130.2, 130.4, 130.5, 130.7, 133.6, 137.7, 157.0, 200.6.

1,1-Dimethylethyl [1-[(4-methylphenyl)methyl]-2-oxopropyl]carbamate (12b): yield (73%); TLC R_f 0.38 (silica gel; hexane:ethyl acetate; 3:1; v/v); ^{1}H NMR ($CDCl_3$) 1.41 (s, 9H), 2.13 (s, 3H), 2.32 (s, 3H), 2.95 (dd, J = 5.9, 14.0 Hz, 1H), 3.05 (dd, J = 6.6, 14.0 Hz, 1H), 4.52 (m, 1H), 5.11 (d, J = 6.6 Hz, 1H), 7.02 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) 21.0, 27.9 28.3, 37.1, 53.4, 60.8, 129.1, 129.4, 132.9, 136.6, 155.2, 207.0; HRMS m/z calcd for $C_{16}H_{23}NO_3$ 278.1756 for (M + H^+), found 278.1753.

Phenylethyl [1-formyl-2-(4-methylphenyl)ethyl]carbamate (12c): yield (81%); TLC R_f 0.27 (silica gel; hexane: ethyl acetate; 3:1; v/v); ^{1}H NMR ($CDCl_3$) 2.31 (s, 3H), 3.10 (dd, J = 2.9, 5.9 Hz, 2H), 4.50 (q, J = 7.4 Hz, 1H), 5.05 (d, J = 7.4 Hz, 1H), 5.11 (s, 2H), 6.97−7.40 (m, 9H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$) 21.0, 35.0, 61.1, 65.4, 127.0, 127.7, 128.1, 128.6, 129.5, 132.2, 136.2, 136.9, 155.9, 199.00; HRMS m/z calcd for $C_{18}H_{19}NO_3$ 298.1443 for (M + H^+), found 298.1447.

Phenylmethyl [1-[(4-methylphenyl)methyl]-2-oxopropyl]carbamate (12d): yield (87%); TLC R_f 0.26 (silica gel; hexane:ethyl acetate; 2:1; v/v); ^{1}H NMR ($CDCl_3$) 2.15 (s, 3H), 2.31 (s, 3H), 2.98 (dd, J = 5.9, 14.0 Hz, 1H), 3.08 (dd,

J = 5.9, 14.0 Hz, 1H), 4.60 (m, 1H), 5.09 (s, 2H), 5.38 (d, J = 7.4 Hz, 1H), 6.99 (d, J = 7.4 Hz, 2H), 7.07 (d, J = 7.4 Hz, 2H), 7.28−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) 21.0, 27.9, 37.1, 61.1, 66.9, 128.0, 128.1, 128.5, 129.0, 129.4, 132.6, 136.3, 136.7, 155.7, 206.3; HRMS *m/z* calcd for $C_{19}H_{21}NO_3$ 312.1600 for (M + H^+), found 312.1597.

***N*-(1-Formylpropyl)-2-naphthalenecarboxamide (12e):** yield (75%); TLC R_f 0.42 (silica gel; hexane:ethyl acetate; 1:1; v/v); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.4 Hz, 3H), 1.86−2.00 (m, 1H), 2.14−2.26 (m, 1H), 4.86 (dd, J = 6.6, 12.4 Hz, 1H), 6.96 (d, J = 7.4 Hz, 1H), 7.54−7.62 (m, 2H), 7.82−7.97 (m, 4H), 8.35 (s, 1H), 9.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.4, 22.3, 60.3, 123.5, 126.9, 127.7, 127.8, 127.8, 128.6, 129.0, 131.0, 132.6, 134.9, 167.4, 199.3; HRMS *m/z* calcd for $C_{15}H_{15}NO_2$ 242.1181 for (M + H^+), found 242.1178.

***N*-[1-Formyl-2-(4-methylphenyl)ethyl]-2-naphthalenecarboxamide (12f):** yield (60%); TLC R_f 0.46 (silica gel; hexane:ethyl acetate; 1:1; v/v); ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.28 (dd, J = 7.4, 14.0 Hz, 1H), 3.38 (dd, J = 5.9, 14.0 Hz, 1H), 4.98 (dd, J = 6.6, 12.5 Hz, 1H), 6.83 (d, J = 5.9 Hz, 1H), 7.08−7.18 (m, 4H), 7.51−7.61 (m, 2H), 7.78−7.93 (m, 4H), 8.27 (s, 1H), 9.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 34.9, 60.3, 123.5, 126.9, 127.8, 127.8, 127.9, 128.6, 129.0, 129.3, 129.6, 130.9, 132.3, 132.6, 135.0, 137.0, 167.3, 198.9; HRMS *m/z* calcd for $C_{21}H_{19}NO_2$ 318.1494 for (M + H^+), found 318.1500.

***N*-(1-Ethyl-2-oxopropyl)-2-naphthalenecarboxamide (12g):** yield (70%); TLC R_f 0.41 (silica gel; hexane:ethyl acetate; 1:1; v/v); ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.82−1.91 (m, 1H), 2.17−2.30 (m, 1H), 2.32 (s, 3H), 4.93 (q, J = 5.9 Hz, 1H), 7.14 (d, J = 5.9 Hz, 1H), 7.53−7.61 (m, 2H), 7.86−7.97 (m, 4H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.9, 24.5, 27.2, 60.0, 123.6, 126.8, 127.6, 127.7, 128.5, 129.0, 131.3, 132.6, 134.9, 167.0, 206.7; HRMS *m/z* calcd for $C_{16}H_{17}NO_2$ 256.1338 for (M + H^+), found 256.1340.

***N*-[1-[(4-Methylphenyl)methyl]-2-oxopropyl]-2-naphthalenecarboxamide (12h):** yield (55%); TLC R_f 0.51 (silica gel; hexane:ethyl acetate; 1:1; v/v); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 2.32 (s, 3H), 3.21 (dd, J = 6.6, 14.0 Hz, 1H), 3.30 (dd, J = 5.2, 14.0 Hz, 1H), 5.1 (dd, J = 6.6, 14.0 Hz, 1H), 6.96 (d, J = 6.6 Hz, 1H), 7.09 (dd, J = 8.1, 13.2 Hz, 4H), 7.53−7.61 (m, 2H), 7.78−7.94 (m, 4H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 28.1, 36.9, 60.1, 123.5, 126.8, 127.6, 127.8, 128.5, 129.0, 129.2, 129.4, 131.1, 132.6, 132.6, 134.9, 136.9, 166.9, 206.3; HRMS *m/z* calcd for $C_{22}H_{21}NO_2$ 332.1651 for (M + H^+), found 332.1654.

***N*-[1-(Cyclohexylcarbonyl)propyl]-2-naphthalenecarboxamide (12i):** yield (32%); TLC R_f 0.42 (silica gel; hexane:ethyl acetate; 3:1; v/v); ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.17−1.37 (m, 4H), 1.48−2.01 (m, 7H), 2.15−2.24 (m, 1H), 2.61−2.68 (m, 1H), 5.04−5.10 (m, 1H), 7.25−7.32 (m, 1H), 7.53−7.61 (m, 2H), 7.83−7.96 (m, 4H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.2, 24.7, 25.2, 25.7, 25.9, 27.5, 29.6, 47.9, 57.9, 123.4, 126.9, 127.8, 127.9, 128.6, 129.0, 131.0, 132.6, 135.0, 167.6, 212.0; HRMS *m/z* calcd for $C_{21}H_{25}NO_2$ 324.1964 for (M + H^+), found 324.1966.

***N*-[2-Cyclohexyl-1-[(4-methylphenyl)methyl]-2-oxoethyl]-2-naphthalenecarboxamide (12j):** yield (27%); TLC R_f 0.48 (silica gel; hexane:ethyl acetate; 3:1; v/v); ^{1}H NMR ($CDCl_3$) δ 1.12−1.32 (m, 4H), 1.40−2.62 (m, 7H), 2.31 (s, 3H), 3.13 (dd, J = 5.9, 14.0 Hz, 1H), 3.27 (dd, J = 6.6, 14.0 Hz, 1H), 5.28 (m, 1H), 7.01−7.12 (m, 5H), 7.52−7.60 (m, 2H), 7.76−7.93 (m, 4H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 25.1, 25.7, 26.0, 27.1, 29.7, 37.4, 48.7, 57.5, 123.5, 126.8, 127.7, 127.8, 127.8, 128.6, 129.0, 129.3, 129.3, 132.6, 134.9, 136.8, 167.1, 211.6; HRMS *m/z* calcd for $C_{27}H_{29}NO_2$ 400.2277 for (M + H^+), found 400.2272.

***N*-(1-Benzoylpropyl)-2-naphthalenecarboxamide (12k):** yield (75%); TLC R_f 0.66 (silica gel; hexane:ethyl acetate; 1:1; v/v); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.8 Hz, 3H), 1.72−1.95 (m, 1H), 2.22−2.30 (m, 1H), 5.85−5.91 (m, 1H), 7.29−7.67 (m, 6H), 7.88−8.06 (m, 4H), 8.07 (d, J = 7.6 Hz, 2H), 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.0, 26.5, 55.3, 123.6, 126.8, 127.6, 127.7, 128.5, 128.5, 128.7, 129.0, 129.0, 131.4, 132.6, 134.0, 134.5, 134.9, 167.1, 199.1; HRMS *m/z* calcd for $C_{21}H_{19}NO_2$ 318.1494 for (M + H^+), found 318.1497.

***N*-[1-[(4-Methylphenyl)methyl]-2-oxo-2-phenylethyl]-2-naphthalenecarboxamide (12l):** yield (51%); TLC R_f 0.71 (silica gel; hexane:ethyl acetate; 1:1; v/v); ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 3.17 (dd, J = 4.4, 14.0 Hz, 1H), 3.49 (dd, J = 5.9, 14.0 Hz, 1H), 6.07−6.13 (m, 1H), 6.85 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 7.20−7.40 (m, 3H), 7.52−7.69 (m, 4H), 7.83−7.95 (m, 3H), 8.06 (d, J = 7.4 Hz, 2H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 38.3, 55.4, 123.6, 126.5, 126.8, 127.7, 127.8, 128.5, 128.5, 128.9, 129.0, 129.1, 129.5, 131.3, 132.3, 132.6, 134.0, 134.7, 134.9, 136.7, 166.8, 198.1; HRMS *m/z* calcd for $C_{27}H_{23}NO_2$ 394.1807 for (M + H^+), found 394.1803.

***N*-(1-Ethyl-2-oxo-4-pentenyl)-2-naphthalenecarboxamide (12o):** yield (63%); TLC R_f 0.38 (silica gel; hexane:ethyl acetate; 3:2; v/v); ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.83 (m, 1H), 1.98 (dd, J = 1.5, 7.4 Hz, 2H), 2.20 (m, 1H), 5.14 (m, 1H), 6.33 (dd, J = 1.5, 15.4 Hz, 2H), 7.13 (m, 1H), 7.50−7.60 (m, 3H), 7.87−7.97 (m, 4H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.9, 18.6, 25.4, 57.4, 123.7, 126.7, 127.5, 127.7, 127.7, 128.5, 129.0, 131.5, 131.5, 132.6, 134.8, 145.6, 166.9, 197.7; HRMS *m/z* calcd for $C_{18}H_{19}NO_2$ 282.1494 for (M + H^+), found 282.1498.

***N*-[1-[(4-Methylphenyl)methyl]-2-oxo-4-pentenyl]-2-naphthalenecarboxamide (12p):** yield (78%); TLC R_f 0.50 (silica gel; hexane:ethyl acetate; 3:2; v/v); ^{1}H NMR ($CDCl_3$) δ 1.96 (dd, J = 1.5, 6.6 Hz, 2H), 2.30 (s, 3H), 3.18 (dd, J = 4.4, 14.0 Hz, 1H), 3.34 (dd, J = 6.6, 14.0 Hz, 1H), 5.35 (m, 1H), 6.30 (dd, J = 1.5, 15.5 Hz, 2H), 6.99−7.15 (m, 6H), 7.51−7.60 (m, 2H), 7.80−7.96 (m, 4H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.6, 21.0, 37.5, 57.6, 123.6, 125.2, 126.7, 127.6, 127.7, 127.7, 128.5, 128.7, 129.0, 129.1, 129.5, 131.4, 131.4, 132.6, 132.6, 134.8, 136.6, 145.7, 166.7, 196.8; HRMS *m/z* calcd for $C_{24}H_{23}NO_2$ 358.1807 for (M + H^+), found 358.1811.

***N*-[1-[[[(1*S*)-1-Formyl-2-phenylethyl]amino]carbonyl]-propyl]-2-naphthalenecarboxamide (15a):** yield (47%, mixture of two diastereomers); TLC R_f 0.43 (silica gel; hexane:ethyl acetate; 1:3; v/v); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.6 Hz, 3H), 1.67−2.01 (m,

4H), 3.05−3.22 (m, 4H), 4.68−4.76 (m, 4H), 6.99−7.30 (m, 14H), 7.43−7.62 (m, 4H), 7.80−7.95 (m, 8H), 8.30 (s, 2H), 9.63 (s, 1H), 9.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.7, 9.9, 25.7, 25.8, 35.0, 35.1, 54.7, 59.8, 123.6, 126.9, 127.1, 127.2, 127.8, 127.9, 128.5, 128.8, 128.8, 129.0, 129.2, 132.6, 135.0, 135.5, 135.7, 167.5, 171.9, 198.4; HRMS *m*/*z* calcd for $C_{24}H_{24}N_2O_3$ 389.1865 for (M + H$^+$), found 389.1870.

***N*-[2-[[(1*S*)-1-Formyl-2-phenylethyl]amino]-1-[(4-methylphenyl)methyl]-2-oxoethyl]-2-naphthalenecarboxamide (15b):** yield (46%, mixture of two diastereomers); TLC R_f 0.63 (silica gel; hexane:ethyl acetate; 1:3; v/v); ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.29 (s, 3H), 2.95−3.20 (m, 8H), 4.59−4.65 (m, 2H), 4.94−4.97 (m, 2H), 6.73−7.35 (m, 22H), 7.45−7.63 (m, 4H), 7.70−7.89 (m, 8H), 8.20 (s, 2H), 9.49 (s, 1H), 9.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 35.0, 54.8, 54.9, 59.7, 123.5, 126.9, 127.8, 127.9, 128.5, 128.7, 128.8, 129.0, 129.2, 129.2, 129.2, 129.3, 129.5, 130.8, 132.6, 133.2, 134.9, 135.5, 136.8, 167.3, 171.3; HRMS *m*/*z* calcd for $C_{30}H_{28}N_2O_3$ 465.2178 for (M + H$^+$), found 465.2175.

***N*-[1-[[[(1*S*)-2-Oxo-1-(phenylmethyl)propyl]amino]carbonyl]propyl]-2-naphthalenecarboxamide (15c):** yield (82%, mixture of two diastereomers); TLC R_f 0.64 (silica gel; ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.64−2.05 (m, 4H), 2.16 (s, 3H), 2.18 (s, 3H), 2.98−3.04 (m, 2H), 3.12−3.21 (m, 2H), 4.65−4.72 (m, 2H), 4.82−4.90 (m, 2H), 6.98−7.30 (m, 14H), 7.50−7.62 (m, 4H), 7.81−7.93 (m, 8H), 8.30 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 9.7, 9.9, 25.8, 25.9, 27.7, 27.9, 37.0, 37.1, 54.7, 54.7, 59.7, 123.6, 126.8, 126.8, 127.1, 127.1, 127.7, 127.8, 128.5, 128.6, 128.7, 129.0, 129.1, 130.9, 132.6, 134.9, 135.8, 136.0, 167.4, 167.4, 171.5, 171.6, 205.9, 206.1; HRMS *m*/*z* calcd for $C_{25}H_{26}N_2O_3$ 403.2016 for (M + H$^+$), found 403.2022.

***N*-[1-[(4-Methylphenyl)methyl]-2-oxo-2-[[(1*S*)-2-oxo-1-(phenylmethyl)propyl]amino]-ethyl]-2-naphthalenecarboxamide (15d):** yield (57%, mixture of two diastereomers); TLC R_f 0.73 (silica gel; ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.08 (s, 3H), 2.30 (s, 6H), 2.88−3.24 (m, 8H), 4.72−4.93 (m, 4H), 6.55−6.62 (m, 2H), 6.86−7.33 (m, 20H), 7.53−7.61 (m, 4H), 7.73−7.95 (m, 8H), 8.19 (s, 1H), 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 27.8, 27.9, 37.1, 37.4, 37.9, 54.8, 55.0, 59.6, 59.7, 123.5, 126.8, 127.0, 127.2, 127.7, 127.8, 127.8, 128.5, 128.6, 128.7, 128.9, 129.0, 129.1, 129.2, 129.4, 130.8, 132.5, 133.2, 134.9, 135.8, 135.8, 136.7, 167.3, 167.3, 170.8, 170.9, 205.6, 206.0; HRMS *m*/*z* calcd for $C_{31}H_{30}N_2O_3$ 479.2335 for (M + H$^+$), found 479.2338.

***N*-[1-[[[(1*S*)-2-[[(1*S*)-1-Formyl-2-phenylethyl]-amino]-1-methyl-2-oxoethyl]amino]carbonyl]propyl]-2-naphthalenecarboxamide (15e):** yield (41%, mixture of four diastereomers); TLC R_f 0.31 (silica gel; ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.88−1.05 (m, 12H), 1.19−1.41 (m, 12H), 1.74−2.02 (m, 8H), 3.09−3.15 (m, 8H), 4.44−4.73 (m, 12H), 6.91−7.30 (m, 32H), 7.51−7.60 (m, 8H), 7.80−7.92 (m, 16H), 8.30 (s, 2H), 8.32 (s, 2H), 9.50 (s, 1H), 9.54 (s, 1H), 9.56 (s, 1H), 9.59 (s, 1H); HRMS *m*/*z* calcd for $C_{27}H_{29}N_3O_4$ 460.2236 for (M + H$^+$), found 460.2241.

4-Methyl-*N*-(2-naphthalenylcarbonyl)phenylalanyl-*N*-[(1*S*)-1-formyl-2-phenylethyl]-L-alaninamide (15f): yield (54%, mixture of four diastereomers); TLC R_f 0.46 (silica gel; ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.15−1.31 (m, 12H), 2.31 (s, 6H), 2.33 (s, 6H), 3.08−3.22 (m, 16H), 4.42−4.90 (m, 12H), 6.82−7.30 (m, 48H), 7.50−7.60 (m, 8H), 7.70−7.93 (m, 16H), 8.21 (s, 4H), 9.55 (s, 2H), 9.61 (s, 1H), 9.63 (s, 1H); HRMS *m*/*z* calcd for $C_{33}H_{33}N_3O_4$ 536.2549 for (M + H$^+$), found 536.2543.

***N*-[1-[[[(1*S*)-1-Methyl-2-oxo-2-[[(1*S*)-2-oxo-1-(phenylmethyl)propyl]amino]ethyl]amino]carbonyl]propyl]-2-naphthalenecarboxamide (15g):** yield (34%, mixture of two diastereomers); TLC R_f 0.35 (silica gel; ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.02−1.07 (m, 6H), 1.30−1.36 (m, 6H), 1.73−2.10 (m, 4H), 2.06 (s, 3H), 2.16 (s, 3H), 2.95−3.18 (m, 4H), 4.46−4.51 (m, 4H), 4.76−4.83 (m, 2H), 6.54−6.62 (m, 1H), 6.70−6.80 (m, 1H), 6.94−7.30 (m, 14H), 7.52−7.62 (m, 4H), 7.82−7.97 (m, 8H), 8.32 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 10.0, 18.0, 25.5, 27.7, 28.0, 36.8, 37.1, 49.2, 55.6, 59.6, 123.5, 126.9, 126.9, 127.7, 127.9, 128.5, 128.5, 128.6, 129.0, 129.0, 129.1, 129.1, 132.6, 135.0, 135.9, 136.3, 167.8, 171.6, 171.6, 175.5, 206.4; HRMS *m*/*z* calcd for $C_{28}H_{31}N_3O_4$ 474.2393 for (M + H$^+$), found 474.2398.

4-Methyl-*N*-(2-naphthalenylcarbonyl)phenylalanyl-*N*-[(1*S*)-2-oxo-1-(phenylmethyl)propyl]-L-alaninamide (15h): yield (31%, mixture of two diastereomers); TLC R_f 0.53 (silica gel; ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.11 (d, J = 7.4 Hz, 3H), 1.22 (d, J = 7.4 Hz, 3H), 2.06 (s, 3H), 2.15 (s, 3H), 2.28 (s, 3H), 2.31 (s, 3H), 2.91−3.25 (m, 8H), 4.35−4.43 (m, 2H), 4.67−4.87 (m, 4H), 6.17 (d, J = 7.4 Hz, 2H), 6.57 (d, J = 6.6 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 6.6 Hz, 2H), 7.00−7.29 (m, 18H), 7.52−7.60 (m, 4H), 7.74−7.93 (m, 8H), 8.22 (s, 1H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 27.7, 29.7, 36.7, 37.0, 49.1, 50.5, 53.4, 59.5, 123.5, 126.9, 127.8, 127.9, 128.5, 128.6, 128.7, 129.1, 129.2, 129.6, 129.6, 132.6, 133.1, 135.0, 136.4, 136.9, 137.0, 167.7, 171.0, 171.4, 206.4; HRMS *m*/*z* calcd for $C_{34}H_{35}N_3O_4$ 550.2706 for (M + H$^+$), found 550.2712.

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Supporting Information Available. Copies of the ^{1}H NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The pK_a of the conjugate acid of BEMP in CH_3CN is 27.6 while in DMSO it is 16.2. The pK_a of the conjugate acid of BTPP in CH_3CN is 28.4 while in DMSO it has been estimated to be 17.0. See, O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. An Efficient Homogeneous Catalytic Enantioselective Synthesis of α-Amino Acid Derivatives. *Tetrahedron Lett.* **1998**, *39*, 8775−8778.

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(18) In cases where UPS alkylations are conducted at sites remote to the Weinreb link, normal solid-phase methodology permits introduction of chiral, nonracemic residues at the C-terminal position. The postcleavage lability of this stereocenter is well established (see references 7a and 7b).

(19) Phenylalanine for the control was determined by subjecting the starting material benzophenone imine of Gly-Ala-Phe-Wang resin to imine hydrolysis, cleavage from the resin, and then tripeptide hydrolysis to give Phe of 97% ee (L/D = 98.5/1.5). The amounts of L-Phe and D-Phe were determined after the alkylations in the same manner as that for the control. The results were as follows: 2 equiv of BEMP and 4-methylbenzyl bromide, 97% ee (L/D = 98.5/1.5); 2 equiv of BTPP and 4-methylbenzyl bromide, 96% ee (L/D = 98/2); 10 equiv of BEMP and ethyl iodide, 93% ee (L/D = 96.5/3.5); 10 equiv of BTPP and ethyl iodide, 84% ee (L/D = 92/8).

(20) For comparison, the pK_a of CH_3CO_2Et is 30−31 in DMSO while that of CH_3CONMe_2 is 34−35. See: Bordwell, F. G.; Fried, H. E. Acidities of the H−C Protons in Carboxylic Esters, Amides, and Nitriles. *J. Org. Chem.* **1981**, *46*, 4327−4331.

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