Pergamon

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Tetrahedron 59 (2003) 1521–1527

TETRAHEDRON

Chain extension of amino acid skeletons: preparation of ketomethylene isosteres

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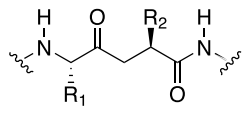
Received 12 September 2002; revised 7 January 2003; accepted 7 January 2003

Abstract—Ketomethylene isosteric replacements for peptide bonds were generated through a zinc carbenoid-mediated chain extension reaction in which a variety of amino acid-derived β-keto esters are converted to γ-keto esters in a single step. The reaction tolerates a variety of protecting groups and amino acid side chains with no epimerization of the amino acid stereocenter.

1. Introduction

Utilization of isosteric replacements for peptide bonds has been an attractive strategy for enzyme inhibition. Successful inhibition of aspartic acid protease targets like HIV-protease and renin has validated the use of ketomethylene (**1**) and hydroxyethylene (**2**) isosteres in peptide systems.[1] However, generation of these peptide mimics has often relied upon lengthy and resource intensive synthetic sequences. The availability of a simple, efficient reaction that facilitates the preparation of heavily functionalized, amino acid-derived γ-keto esters would find utility in the preparation of these isosteres, regardless of the inhibition target. Furthermore, identification of a flexible and efficient synthetic method or strategy amenable to the incorporation of these isosteres into a peptide fragment immobilized on a solid support would facilitate the general development and study of peptide isosteres (Fig. 1).



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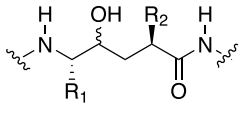

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Figure 1. Peptide isosteric replacements.

From a synthetic chemistry viewpoint, the aim of the proposed research was the adaptation of a synthetic method discovered in our laboratories for the simple and efficient conversion of β-keto esters (**3**) to γ-keto esters (**7**) through a one-pot, zinc-mediated chain extension reaction (Scheme 1).[2] Treatment of β-keto esters, amides, and phosphonates with the electrophilic Furukawa reagent, ethyl(iodomethyl)-zinc, results in efficient generation of the chain extended species. However, chain extension of substrates that contained ancillary Lewis basic functionality had not yet been studied. A report[3] that implicated the Furukawa reagent in the methylation of an amide's nitrogen suggested that the direct application of this chain extension methodology to amino acid-derived substrates may be challenging. Furthermore, utilization of basic reagents with amino acid substrates presents the potential for epimerization of the critical stereocenter. With these concerns we undertook the study of the zinc-mediated chain extension of amino acid derived β-keto esters.

2. Results and discussion

A variety of amino acids were selected as starting materials, although the primary focus of the study were amino acids with aliphatic and aromatic side chains. Racemic amino acids were utilized to establish the chemical efficiency of the reaction sequence, at which time a sampling of L-amino acids were used to establish the stereochemical integrity of the procedure. A diverse group of nitrogen protecting groups was chosen, including carbamate groups Cbz,[4] Boc,[5] and Fmoc,[6] as well as an amide group (Bz) designed to mimic the presence of a peptide bond.

The typical strategy by which the C-terminus is manipulated is illustrated in Scheme 2. After *N*-protection of the amino

Keywords: isostere; zinc; carbenoid; peptide mimic; chain extension.

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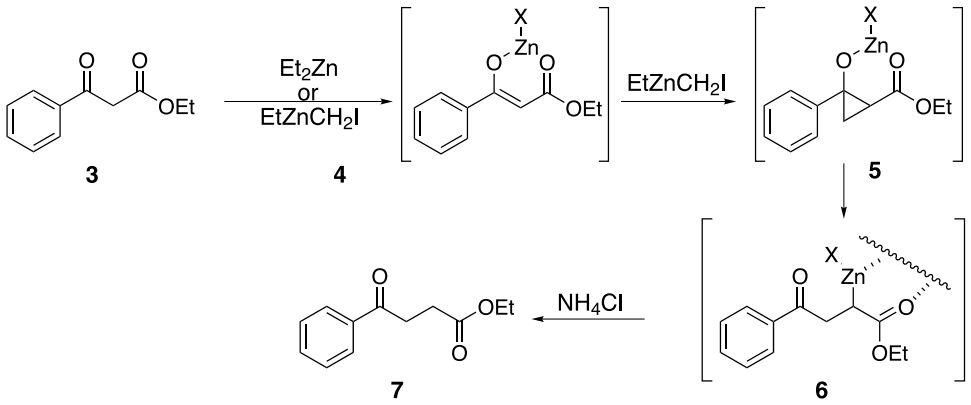
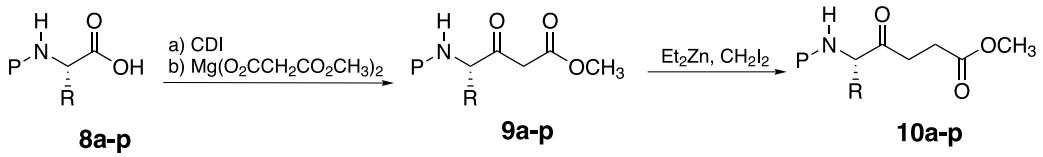
0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00052-8



Scheme 1. Zinc-mediated chain extension.



Scheme 2. γ-Keto ester formation.

acids, the corresponding β-keto esters **9** were formed via the neutral *C*-acylation reaction of acyl imidazoles as described by Masamune and Brooks.[7] Conversion of *N*-protected amino acids to β-keto esters using a similar method[8] at elevated temperatures resulted in the formation of 12–16% of the racemate. However, the simplicity of the Masamune procedure made it the most attractive option for generation of the chain extension substrates. The results of the β-keto ester formation are summarized in Table 1. The reactions to provide β-keto methyl esters **9** were relatively slow, possibly due to the heterogeneous nature of the monomethyl malonate complex in THF. Reaction times of one to two days were required in order to get maximum yields of 50–75%. When methylene chloride was used as the solvent, improved solubility of malonate complex was observed. Initial formation of β-keto ester in 40% yield was observed, yet a reaction time of two days was required in order to optimize the yield. Monobenzyl malonate (R″=Bn) was used in the sequence described in Scheme 3. This reaction was homogenous in THF and commonly proceeded to 50–75% yields after one day stirring at room temperature. While Cbz, Boc, and Bz protected amino acids were easily converted to the β-keto esters, Fmoc-protected amino acids degraded slowly during the acylation procedure.

Table 1. Two-step generation of amino acid-derived γ-keto methyl esters

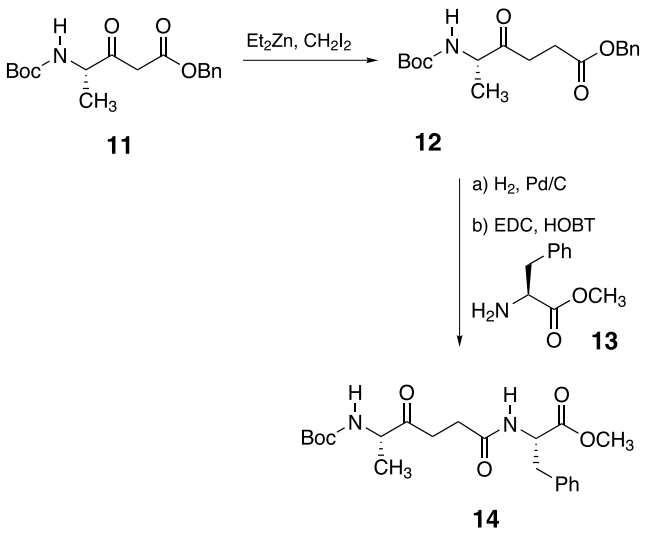
SM[a]	P	R	Yield of **9**[b]	Yield of **10**[b]
8a	Boc	H	91	25
8b	Boc	Me	70	48
8c	Boc	Ph	41	57
8d	Boc	Bn	63	49
8e	Cbz	H	65	60
8f	Cbz	Me	66	60
8g	Cbz	Ph	45	48
8h	Cbz	Bn	71	68
8i	Bz	H	65	58
8j	Bz	Me	47	58
8k	Bz	Ph	28	43
8l	Bz	Bn	74	58
8m	Fmoc	H	65	55
8n	Fmoc	Me	76	57
8o	Fmoc	Ph	85	63
8p	Fmoc	Bn	67	68

[a] Starting material.
[b] Isolated yield (%) of purified material.

After formation of the β-keto esters, the chain extension reaction was performed by exposure of the β-keto ester **9** to the carbenoid. The typical chain extension reaction utilized excess carbenoid generated from 5.0 equiv. of Et_2Zn and 7.5 equiv. of methylene iodide in a solvent of methylene chloride. The derivatized amino acid was added as a solution in methylene chloride and the resulting solution monitored for consumption of starting β-keto ester by TLC. Every amino acid derivative underwent the chain extension reaction, although differences in efficiency were observed.[†] In a few instances, unreacted starting material was identified in the crude reaction mixture. Similar retention factors, which required careful chromatographic separation, were observed for the starting material and chain-extended products. This resulted in diminished isolated yields. The fate of the remaining starting material is unclear, although intermolecular aldol reactions have been observed in other reactions of this type.[9]

A number of features of zinc-mediated chain extension reaction are noteworthy. The protective groups were not degraded by these reactions. Even the base sensitive Fmoc group tolerated the reaction conditions. The presence of a modestly acidic amide or carbamate proton (NH) does not negatively affect the chain extension reaction. It is unclear whether the NH is deprotonated in the reaction, although the required use of 5 equiv. of carbenoid suggests that the amide or carbamate protons may consume some of the reagent. It is

[†] The products, following purification by column chromatography, were one spot by TLC analysis and possessed clean ^{13}C NMR spectra.



Scheme 3. Tripeptide mimic.

also possible that the amide or carbamate protons could serve to quench the intermediate enolate (**6**) generated after chain extension. Regardless of the role of the NH, it is clear that the presence of modestly acidic functionality is tolerated in the reaction.

Methylation of the amide or carbamate nitrogen was not observed, although extended exposure of the amino acid substrate to the carbenoid may result in partial methylation. Control of reaction time and carbenoid equivalents was sufficient to prevent *N*-methylation.

Modest variation in the efficiency of the reaction was observed with respect to the different protecting groups. While the Cbz and Bz protecting groups appeared to tolerate the reaction conditions quite well, the Boc groups appeared to be somewhat labile under these Lewis acidic conditions. Although chain-extended products were formed from the Boc-protected amino acids, the yields were usually lower than reactions performed on analogous Cbz-protected amino acids. The efficient conversion of amide-protected (Bz) amino acids bodes well for polypeptide substrates.

Successful chain extension has been observed for all of the amino acid substrates studied to this point, however the Boc-glycine substrate reacts with the least efficiency. No clear picture has arisen which can explain this diminished reactivity, although the intermediate enolate reagent appears to have limited stability and undergoes further reaction/decomposition to provide unidentifiable products. The reaction time was shortened (with a concomitant cost in yield) in order to obtain clean product.

Epimerization of the amino acid stereocenter would diminish dramatically the attractiveness of the proposed approach to ketomethylene isosteres. In order to probe the integrity of the stereocenters, a single enantiomer of selected amino acids was selected and transformed to the γ-keto esters using the sequence of reactions described above. The β-keto esters and γ-keto esters were compared on a Daicel Chiralpak® AD-RH reverse phase chiral column. Approximately 5–7% racemization was observed in the γ-keto esters, although comparison to the β-keto ester starting materials revealed that this epimerization took place during formation of the β-keto ester. No observation of amino acid epimerization during the zinc-mediated chain extension reaction was observed.

As a further demonstration of the utility of the zinc-mediated reaction we have successfully prepared **14**, a γ-keto amide functionality that is flanked by two amino acids (Scheme 3). Treatment of β-keto ester **11** with the zinc-carbenoid provided access to the targeted γ-keto ester **12**. Cleavage of the benzyl ester, followed by EDC coupling with the methyl ester of phenylalanine **13** yielded the tripeptide mimic **14**. No epimerization of amino acid stereocenters was observed during analysis of the product by NMR or by chiral HPLC.

3. Conclusion

Amino acid derived β-keto esters have been successfully chain extended to provide their γ-keto ester analogues. These products have the requisite structural features to find use as ketomethylene isosteric replacements for peptide bonds. No amino acids with polar side chains, heterocyclic rings, or olefinic functionality have been included in this study. However, the compatibility of the zinc-mediated chain extension method with olefinic functionality[2] and with the Lewis basic functionality present in the peptide substrates suggest that the chain extension reaction should have broad applicability. Furthermore, the ease with which the substrates can be prepared presents this method as an attractive alternative to established approaches to these functional groups. The extension of this methodology to additional amino acid derivatives, including those with polar side chains, is being studied and will be reported in the future.

4. General experimental

All reactions were run in oven-dried glassware under nitrogen atmosphere and stirred with teflon-coated magnetic stir-bars. The terms concentrated in vacuo or under reduced pressure refer to the use of a rotary-evaporator. Methylene chloride was distilled from phosphorous pentoxide. Ethyl acetate and hexanes were distilled prior to use. Reagents were purchased from commercial suppliers and used without further purification. Diethyl zinc was used as a 1.0 M solution in hexanes as supplied by Aldrich. Methylene iodide (CH_2I_2) was purchased from commercial suppliers and non-oxidized copper wire was added as a stabilizer. Column chromatography was performed on EM Science flash silica gel (35–75 μm). Mobile phases were used as noted. Thin layer chromatography (TLC) was carried out on EM Science F254 glass plates and visualized by UV and anisaldehyde or phosphomolybdic acid stains. Low resolution mass spectroscopy was performed by the University of New Hampshire Instrumentation Center on a Perkin–Elmer 2400 Analyzer. High resolution mass spectroscopy was performed at Merck Pharmaceutical Research, West Point, PA.

4.1. Representative procedures

4.1.1. Formation of the β-keto ester: methyl 4-(carbobenzyloxy)amino-3-oxo-5-phenyl-pentanoate (9h). Into a 25 mL round-bottomed flask equipped with a stir bar were placed 300 mg (1.00 mmol) Cbz-phenylalanine (**8h**) and 10 mL anhydrous THF. Carbonyl diimidazole (CDI) 178 mg (1.10 mmol) was added and the solution stirred approximately 15 min. In a separate 100 mL round-bottom flask which contained a solution of monomethyl malonate (352 mg, 3.00 mmol) in 30 mL of anhydrous THF was added 1.50 mL (1.50 mmol) of a 1 M hexane solution of dibutylmagnesium at 0°C. This solution, which appears as a white slurry, was allowed to warm to room temperature. The acyl imidazole solution was transferred to the flask which contained the magnesium salt and the reaction was monitored by TLC. The solution was allowed to stir for 48 h and quenched by the addition of 30 mL sat. aq. NH_4Cl solution. The solution was extracted three times with 20 mL Et_2O. The combined organics were dried with $MgSO_4$, filtered, and concentrated. The crude residue was chromatographed on silica with 15% EtOAc in hexanes to yield 252 mg (71%) of **9h** as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39–7.23 (m, 8H), 7.15 (m, 2H), 5.35 (d, 1H, J=7.7 Hz), 5.12 (s, 2H), 4.67 (dd, 1H, J=7.0, 13.8 Hz), 3.70 (s, 3H), 3.55–3.43 (AB, 2H, J=16 Hz), 3.19–3.14 (AX, 1H, J=6.1, 6.1 Hz), 3.04–2.98 (BX, 1H, J=7.1, 7.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.6, 167.3, 155.8, 136.2, 135.8, 129.2, 128.8, 128.5, 128.2, 128.1, 127.2, 67.1, 60.8, 52.4, 46.7, 36.9. HRMS (M+Na^+) calcd for $C_{20}H_{21}NO_5Na$ 378.1312, found 378.1305.

4.1.2. Zinc-mediated chain extension: methyl 5-(carbobenzyloxy)amino-4-oxo-6-phenyl-hexanoate (10h). A 50 mL round-bottomed flask was charged with 30 mL anhydrous CH_2Cl_2 and 255 μL (3.16 mmol) of methylene iodide was added. The solution was cooled to 0°C and 2.11 mL (2.11 mmol) of a 1 M solution of diethylzinc in hexanes was added slowly. The ice bath was removed immediately and a white precipitate formed rapidly. After stirring for 2 min, 150 mg (0.42 mmol) of **9h** dissolved in 5 mL CH_2Cl_2 was added and the reaction monitored by TLC (normal phase). The product spot appeared at a slightly higher R_f than starting material and was best visualized by staining the TLC plates with anisaldehyde. The reaction was complete after 30 min and was quenched with 25 mL sat. aq. NH_4Cl solution. The organic solution was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography on silica using 15% EtOAc in hexane provided 106 mg (68%) of **10h** as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38–7.14 (m, 10H), 5.38 (d, 1H, J=7.3 Hz), 5.08 (s, 2H), 4.64 (q, 1H, J=6.6 Hz), 3.67 (s, 3H), 3.16 (dd (A of ABX), 1H, J=6.4, 14.1 Hz), 2.99 (dd (B of ABX), 1H, J=6.9, 14.1 Hz), 2.81–2.74 (m, 2H), 2.60–2.57 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.0, 173.0, 156.0, 136.2, 135.9, 129.2, 128.7, 128.5, 128.2, 128.1, 127.1, 66.9, 60.5, 51.8, 37.4, 35.1, 27.5. HRMS (M+Na^+) calcd for $C_{21}H_{23}NO_5Na$ 392.1474, found 392.1477.

4.2. Characterization data for Table 1

4.2.1. Methyl 4-(carboxy-*t*-butyl)-amino-3-oxo-butanoate (9a). 91%. Yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.22 (bs, 1H), 4.11 (d, 2H, J=5.1 Hz), 3.72 (s, 3H), 3.49 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.6, 167.0, 155.6, 80.1, 52.5, 50.5, 46.2, 28.2. HRMS (M+Na^+) calcd for $C_{10}H_{17}NO_5Na$ 254.1104, found 254.1108.

4.2.2. (±)-Methyl 4-(carboxy-*t*-butyl)-amino-3-oxo-pentanoate (9b). 70%. White solid; mp 52–54°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.15 (bs, 1H), 4.36 (dq, 1H, J=7.0, 7.0 Hz), 3.73 (s, 3H), 3.57 (AB, 2H, J=15.8 Hz), 1.43 (s, 9H), 1.36 (d, 3H, J=7.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.3, 167.5, 155.3, 80.0, 55.3, 52.4, 45.5, 28.2, 16.9. HRMS (M+Na^+) calcd for $C_{11}H_{19}NO_5Na$ 268.1161, found 268.1157.

4.2.3. (±)-Methyl 4-(carboxy-*t*-butyl)-amino-3-oxo-4-phenylbutanoate (9c). 41%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54–7.29 (m, 5H), 5.82 (bs, 1H), 5.44 (m, 1H), 3.65 (s, 3H), 3.50–3.31 (AB, 2H, J=16.0 Hz), 1.40 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 166.6, 154.7, 135.7, 129.3, 128.8, 128.1, 80.1, 64.4, 52.4, 45.8, 28.2. HRMS (M+Na^+) calcd for $C_{16}H_{21}NO_5Na$ 330.1312, found 330.1314.

4.2.4. (±)-Methyl 4-(carboxy-*t*-butyl)-amino-3-oxo-5-phenylpentanoate (9d). 63%. White solid; mp 78–79°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33–7.16 (m, 5H), 5.02 (m, 1H), 4.56 (dt, 1H, J=7.2, 7.2 Hz), 3.71 (s, 3H), 3.49 (AB, 2H, J=16.0 Hz), 3.06 (AB, 2H, J=6.0, 14.0 Hz), 1.40 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.8, 167.3, 155.2, 136.0, 129.2, 128.7, 127.0, 80.2, 60.4, 52.4, 46.6, 36.9, 28.2. HRMS (M+H^+) calcd for $C_{17}H_{24}NO_5$ 322.1649, found 322.1668.

4.2.5. Methyl 4-(carboxybenzyl)-amino-3-oxo-butanoate (9e). 65%. Yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 736 (m, 5H), 5.41 (bs, 1H), 5.13 (s, 2H), 4.22 (d, 2H, J=5.0 Hz), 3.75 (s, 3H), 3.51 (s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 166.7, 156.2, 136.2, 128.5, 128.2, 128.1, 67.1, 52.6, 50.8, 46.2. HRMS (M+Na^+) calcd for $C_{13}H_{15}NO_5Na$ 288.0848, found 288.0855.

4.2.6. (±)-Methyl 4-(carboxybenzyl)-amino-3-oxo-pentanoate (9f). 66%. Yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.72 (d, 1H, J=7.1 Hz), 5.08 (s, 2H), 4.46–4.38 (s, 2H), 3.68 (s, 3H), 3.60–3.47 (m, 2H), 1.33 (d, 3H, J=7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.0, 167.3, 155.8, 136.2, 128.5, 128.2, 128.0, 67.0, 55.8, 52.4, 45.5, 16.8. HRMS (M+Na^+) calcd for $C_{14}H_{17}NO_5Na$ 302.1004, found 302.1008.

4.2.7. (±)-Methyl 4-(carboxybenzyl)-amino-3-oxo-4-phenylbutanoate (9g). 45%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38–7.26 (m, 10H), 6.14 (bs, 1H), 5.52 (m, 1H), 5.13–5.00 (AB, 2H), 3.66 (s, 3H), 3.51–3.32 (AB, 2H, J=12.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 197.7, 166.5, 155.2, 136.0, 135.3, 129.4, 129.4, 129.0, 128.5, 128.1, 128.1, 67.1, 64.6, 52.5, 45.7. HRMS (M+Na^+) calcd for $C_{19}H_{19}NO_5Na$ 364.1155, found 364.1171.

4.2.8. (±)-Methyl 4-(carboxybenzyl)-amino-3-oxo-5-phenylpentanoate (9h). 71%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39–7.23 (m, 8H), 7.15 (m, 2H), 5.35 (d, 1H, J=7.7 Hz), 5.12 (s, 2H), 4.67 (dd, 1H, J=7.0,

13.8 Hz), 3.70 (s, 3H), 3.55–3.43 (AB, 2H, J=16 Hz), 3.19–3.14 (AX, 1H, J=6.1, 6.1 Hz), 3.04–2.98 (BX, 1H, J=7.1, 7.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.6, 167.3, 155.8, 136.2, 135.8, 129.2, 128.8, 128.5, 128.2, 128.1, 127.2, 67.1, 60.8, 52.4, 46.7, 36.9. HRMS (M+Na^+) calcd for $C_{20}H_{21}NO_5Na$ 378.1312, found 378.1305.

4.2.9. Methyl 4-(*N*-benzoyl)-amino-3-oxo-butanoate (9i). 65%. White solid; mp 83–86°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.55–7.43 (m, 3H), 6.93 (bs, 1H), 4.47 (d, 2H, J=4.7 Hz), 3.76 (s, 3H), 3.59 (2, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.1, 167.3, 166.9, 133.5, 131.9, 128.6, 127.1, 56.2, 49.9, 46.5. HRMS (M+H^+) calcd for $C_{12}H_{14}NO_4$ 236.0923, found 236.0919.

4.2.10. (±)-Methyl 4-(*N*-benzoyl)-amino-3-oxo-pentanoate (9j). 47%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.80–7.76 (m, 2H), 7.52–7.38 (m, 3H), 7.11 (d, 1H, J=6.5 Hz), 4.85 (dt, 1H, J=7.1, 14.2 Hz), 3.70 (s, 3H), 3.63 (AB, 2H, J=15.9 Hz), 1.41 (d, 3H, J=7.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.9, 167.3, 166.9, 133.5, 131.8, 128.6, 127.0, 54.7, 52.5, 45.7, 16.8. HRMS (M+H^+) calcd for $C_{13}H_{16}NO_4$ 250.1079, found 250.1081.

4.2.11. (±)-Methyl 4-(*N*-benzoyl)-amino-3-oxo-4-phenylbutanoate (9k). 28%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.52–7.33 (m, 10H), 5.90 (d, 1H, J=6.1 Hz), 3.67 (s, 3H), 3.52 (AB, 2H, J=15.4 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 166.5, 166.3, 135.3, 133.5, 131.8, 129.4, 129.0, 128.5, 128.3, 127.1, 63.5, 52.5, 45.9. HRMS (M+H^+) calcd for $C_{18}H_{18}NO_4$ 334.1046, found 334.1050.

4.2.12. (±)-Methyl 4-(*N*-benzoyl)-amino-3-oxo-5-phenylpentanoate (9l). 74%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.51 (m, 1H), 7.39 (m, 2H), 7.32–7.19 (m, 5H), 6.87 (d, 1H, J=7.2 Hz), 5.10 (dt, 1H, J=6.9, 7.2 Hz), 3.69 (s, 3H), 3.56 (AB, 2H, J=15.9 Hz), 3.21 (ABX, 2H, J=6.4, 14.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.2, 167.2, 167.1, 135.8, 133.4, 131.9, 129.2, 128.8, 128.6, 127.2, 127.0, 59.6, 52.4, 46.8, 36.6. HRMS (M+Na^+) calcd for $C_{19}H_{19}NO_4Na$ 348.1206, found 348.1211.

4.2.13. Methyl 4-(carboxy-9-fluorenylmethyl)-amino-3-oxo-butanoate (9m). 65%. White solid; mp 115–117°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.59 (m, 2H), 7.42–7.29 (m, 4H), 5.63 (m, 1H), 4.44 (m, 2H), 4.21 (m, 3H), 3.73 (s, 3H), 3.49 (s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 167.1, 156.2, 143.7, 141.3, 127.7, 127.1, 125.0, 120.0, 67.1, 52.6, 50.8, 47.1, 46.2. HRMS (M+Na^+) calcd for $C_{20}H_{19}NO_5Na$ 376.1161, found 376.1153.

4.2.14. (±)-Methyl 4-(carboxy-9-fluorenylmethyl)-amino-3-oxo-pentanoate (9n). 76%. White solid; mp 105–107°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.59 (m, 2H), 7.42–7.29 (m, 4H), 5.52 (bs, 1H), 4.48–4.38 (m, 3H), 4.23–4.19 (m, 1H), 3.73 (s, 3H), 3.55 (m, 2H), 1.39 (d, 3H, J=7.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.1, 167.0, 155.8, 143.7, 141.3, 127.7, 127.1, 125.0, 120.0, 66.9, 55.8, 52.5, 47.1, 45.5, 17.0. HRMS (M+Na^+) calcd for $C_{21}H_{21}NO_5Na$ 390.1317, found 390.1314.

4.2.15. (±)-Methyl 4-(carboxy-9-fluorenylmethyl)-amino-3-oxo-4-phenylbutanoate (9o). 85%. White solid; mp 139–142°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.77–7.75 (m, 2H), 7.58–7.56 (m, 2H), 7.42–7.26 (m, 9H), 6.16 (d, 1H, J=5.7 Hz), 5.54 (d, 1H, J=6.3 Hz), 4.42–4.30 (m, 2H), 4.21–4.18 (m, 1H), 3.68 (s, 3H), 3.44 (AB, 2H, J=15.7 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 197.8, 166.4, 155.2, 143.8, 141.2, 135.3, 129.4, 129.1, 128.1, 127.7, 127.0, 125.0, 119.9, 67.1, 64.6, 52.5, 47.1, 45.7. HRMS (M+Na^+) calcd for $C_{26}H_{23}NO_5Na$ 452.1474, found 452.1479.

4.2.16. (±)-Methyl 4-(carboxy-9-fluorenylmethyl)-amino-3-oxo-5-phenylpentanoate (9p). 67%. White solid; mp 75–78°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.55 (m, 2H), 7.42 (m, 2H), 7.31–7.24 (m, 5H), 7.16 (m, 2H), 5.48 (d, 1H, J=7.81 Hz), 4.67 (dt, 1H, J=7.6, 7.8 Hz), 4.46–4.38 (m, 2H), 4.20–4.15 (m, 1H), 3.71 (s, 3H), 3.49 (AB, 2H, J=16 Hz), 3.19 (A of AB, 1H, J=6.0, 14.0 Hz), 3.00 (B of AB, 1H, J=7.5, 14.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.4, 167.2, 155.8, 143.7, 141.3, 135.9, 129.3, 128.8, 127.8, 127.2, 127.1, 125.0, 120.0, 66.9, 60.8, 52.5, 47.2, 46.6, 36.7. HRMS (M+Na^+) calcd for $C_{27}H_{25}NO_5Na$ 466.1625, found 466.1617.

4.2.17. Methyl 5-(carboxy-*t*-butyl)-amino-4-oxo-pentanoate (10a). Reaction time 5 min. 25%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.06 (m, 1H), 3.67 (s, 3H), 2.74–2.62 (m, 4H), 1.43 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 204.2, 172.8, 155.6, 79.8, 51.8, 50.2, 34.3, 28.2, 27.5. HRMS (M+Na^+) calcd for $C_{11}H_{19}NO_5Na$ 268.1161, found 268.1165.

4.2.18. (±)-Methyl 5-(carboxy-*t*-butyl)-amino-4-oxo-hexanoate (10b). 48%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.21 (bs, 1H), 4.34 (dt, 1H, J=6.2, 6.2 Hz), 3.68 (s, 3H), 2.91–2.56 (m, 4H), 1.44 (s, 9H), 1.36 (d, 3H, J=6.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.8, 173.2, 155.1, 79.9, 55.0, 51.8. 33.6, 28.3, 27.5, 17.7. HRMS (M+Na^+) calcd for $C_{12}H_{21}NO_5Na$ 282.1317, found 282.1312.

4.2.19. (±)-Methyl 5-(carboxy-*t*-butyl)-amino-4-oxo-5-phenylpentanoate (10c). 57%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 5.86 (bs, 1H), 5.33 (d, 1H, J=5.4 Hz), 3.65 (s, 3H), 2.81–2.46 (m, 4H), 1.40 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 204.3, 172.6, 154.8, 136.8, 129.1, 128.5, 127.8, 79.9, 64.1, 51.8, 34.3, 28.2, 27.6. HRMS (M+Na^+) calcd for $C_{17}H_{23}NO_5Na$ 322.1648, found 322.1655.

4.2.20. (±)-Methyl 5-(carboxy-*t*-butyl)-amino-4-oxo-6-phenylhexanoate (10d). 49%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33–7.25 (m, 4H), 7.19 (m, 1H), 5.05 (bs, 1H), 4.54 (m, 1H), 3.68 (s, 3H), 3.16–3.10 (AX, 1H, J=7.1, 14.0 Hz), 2.98–2.93 (BX, 1H, J=7.0, 13.9 Hz), 2.78–2.69 (m, 2H), 2.60–2.56 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.4, 172.9, 155.1, 136.2, 129.2, 128.6, 126.9, 80.0, 60.1, 51.8, 37.5, 35.1, 28.2, 27.5. HRMS (M+Na^+) calcd for $C_{18}H_{25}NO_5Na$ 358.1625, found 358.1635.

4.2.21. Methyl 5-(carboxybenzyl)-amino-4-oxo-pentanoate (10e). 60%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ

7.36–7.30 (m, 5H), 5.46 (bs, 1H), 5.12 (s, 2H), 4.16 (m, 2H), 3.68 (s, 3H), 2.75–2.68 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 203.7, 172.8, 156.1, 136.2, 128.5, 128.1, 128.0, 67.0, 51.9, 50.6, 40.2, 34.3, 27.5. HRMS (M+H$^+$) calcd for $C_{14}H_{18}NO_5$ 280.1185, found 280.1180.

4.2.22. (±)-Methyl 5-(carboxybenzyl)-amino-4-oxo-hexanoate (10f). 60%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 5.51 (bs, 1H), 5.11 (s, 2H), 4.43 (dq, 1H, J=7.1 Hz), 3.68 (s, 3H), 2.94–2.59 (m, 4H), 1.41 (d, 3H, J=7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.6, 172.9, 155.7, 136.1, 128.5, 128.1, 128.0, 66.9, 55.5, 51.8, 33.7, 28.7, 27.5, 17.6. HRMS (M+H$^+$) calcd for $C_{15}H_{20}NO_5$ 294.1341, found 294.134147.

4.2.23. (±)-Methyl 5-(carboxybenzyl)-amino-4-oxo-5-phenylpentanoate (10g). 48%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40–7.33 (m, 10H), 6.16 (bs, 1H), 5.39 (d, 1H, J=6.1 Hz), 5.05 (AB, 2H, J=12.2 Hz), 3.67 (s, 3H), 2.73–2.51 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 204.0, 172.5, 155.5, 136.5, 136.2, 133.1, 129.2, 128.7, 128.5, 128.1, 127.9, 66.9, 64.5, 51.8, 34.3, 27.6. HRMS (M+H$^+$) calcd for $C_{20}H_{21}NO_5$ 356.1492, found 356.1491.

4.2.24. (±)-Methyl 5-(carboxybenzyl)-amino-4-oxo-6-phenylhexanoate (10h). 68%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38–7.14 (m, 10H), 5.38 (d, 1H, J=7.3 Hz), 5.08 (s, 2H), 4.64 (q, 1H, J=6.6 Hz), 3.67 (s, 3H), 3.16 (dd (A of AB), 1H, J=6.4, 14.1 Hz), 2.99 (dd (B of AB), 1H, J=6.9, 14.1 Hz), 2.81–2.74 (m, 2H), 2.60–2.57 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.0, 173.0, 156.0, 136.2, 135.9, 129.2, 128.7, 128.5, 128.2, 128.1, 127.1, 66.9, 60.5, 51.8, 37.4, 35.1, 27.5. HRMS (M+Na$^+$) calcd for $C_{21}H_{23}NO_5Na$ 392.1468, found 392.1472.

4.2.25. Methyl 5-(*N*-benzoyl)-amino-4-oxo-pentanoate (10i). 58%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.83–7.75 (m, 2H), 7.55–7.41 (m, 3H), 6.93 (bs, 1H), 4.42 (d, 2H, J=4.5 Hz), 3.70 (s, 3H), 2.88–2.70 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 203.9, 172.8, 167.2, 133.7, 131.7, 128.6, 127.0, 51.9, 49.6, 34.6, 27.6. HRMS (M+Na$^+$) calcd for $C_{13}H_{15}NO_4Na$ 272.0899, found 272.0907.

4.2.26. (±)-Methyl 5-(*N*-benzoyl)-amino-4-oxo-hexanoate (10j). 58%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2H), 7.53–7.42 (m, 3H), 7.02 (d, 1H, J=6.3 Hz), 4.85 (dq, 1H, J=7.0, 7.0 Hz), 3.68 (s, 3H), 3.01–2.61 (m, 4H), 1.52 (d, 3H, J=7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.9, 173.0, 166.6, 134.0, 131.7, 128.5, 127.0, 54.4, 51.9, 33.8, 27.6, 17.6. HRMS (M+Na$^+$) calcd for $C_{14}H_{17}NO_4Na$ 286.1055, found 286.1049.

4.2.27. (±)-Methyl 5-(*N*-benzoyl)-amino-4-oxo-5-phenylpentanoate (10k). 43%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.55–7.33 (m, 9H), 5.79 (d, 1H, J=6.1 Hz), 3.65 (s, 3H), 2.90–2.50 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 204.6, 172.8, 166.5, 136.5, 133.9, 131.7, 129.3, 128.7, 128.5, 128.1, 127.1, 63.3, 52.0, 34.5, 27.7. HRMS (M+Na$^+$) calcd for $C_{19}H_{19}NO_4Na$ 348.1206, found 348.1199.

4.2.28. (±)-Methyl 5-(*N*-benzoyl)-amino-4-oxo-6-phenylhexanoate (10l). 58%. Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.51–7.20 (m, 8H), 6.77 (d, 1H, J=6.8 Hz), 5.07 (dt, 1H, J=6.6, 6.6 Hz), 3.68 (s, 3H), 3.23 (ABX, 2H, J=6.7, 14.1 Hz), 2.83 (m, 2H), 2.62 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.8, 173.2, 166.8, 136.0, 133.9, 131.8, 129.3, 128.7, 128.6, 127.1, 126.9, 59.3, 51.9, 37.2, 35.2, 27.6. HRMS (M+Na$^+$) calcd for $C_{20}H_{21}NO_4Na$ 362.1363, found 362.1364.

4.2.29. Methyl 5-(carboxy-9-fluorenylmethyl)-amino-4-oxo-pentanoate (10m). 55%. White solid; mp 65–68°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.60 (m, 2H), 7.42–7.29 (m, 4H), 5.56 (bs, 1H), 4.40 (m, 2H), 4.27 (m, 1H), 4.15 (m, 2H), 3.68 (s, 3H), 2.73–2.66 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 204.0, 172.8, 156.2, 143.9, 141.3, 127.7, 127.0, 125.1, 119.9, 67.1, 52.2, 50.6, 47.1, 34.3, 27.5. HRMS (M+H$^+$) calcd for $C_{21}H_{22}NO_5$ 368.1498, found 368.1497.

4.2.30. (±)-Methyl 5-(carboxy-9-fluorenylmethyl)-amino-4-oxo-hexanoate (10n). 57%. White solid; mp 95–97°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.60 (m, 2H), 7.42–7.30 (m, 4H), 5.56 (bs, 1H), 4.45–4.35 (m, 3H), 4.22 (m, 1H), 3.68 (s, 3H), 2.92–2.59 (m, 4H), 1.42 (d, 3H, J=7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.7, 173.0, 155.8, 144.0, 141.3, 127.7, 127.0, 125.0, 120.0, 66.8, 55.5, 51.9, 47.1, 33.7, 27.5, 17.8. HRMS (M+H$^+$) calcd for $C_{22}H_{24}NO_5$ 382.1654, found 382.1661.

4.2.31. (±)-Methyl 5-(carboxy-9-fluorenylmethyl)-amino-4-oxo-5-phenylpentanoate (10o). 63%. White solid; mp 110–115°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.56 (m, 2H), 7.41–7.21 (m, 9H), 6.21 (m, 1H), 5.41 (m, 1H), 4.40–4.29 (m, 2H), 4.21–4.17 (m, 1H), 3.64 (s, 3H), 2.81–2.48 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 204.0, 172.5, 155.8, 143.8, 141.2, 136.3, 129.3, 128.8, 127.9, 127.6, 127.0, 125.0, 119.9, 67.0, 64.5, 51.9, 47.1, 34.3, 27.2. HRMS (M+H$^+$) calcd for $C_{27}H_{26}NO_5$ 444.1811, found 444.1815.

4.2.32. (±)-Methyl 5-(carboxy-9-fluorenylmethyl)-amino-4-oxo-6-phenylhexanoate (10p). 68%. White solid; mp 108–110°C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.55 (m, 2H), 7.42 (m, 2H), 7.31–7.24 (m, 5H), 7.16 (m, 2H), 5.48 (d, 1H, J=7.81 Hz), 4.67 (dt, 1H, J=7.6, 7.8 Hz), 4.43–4.33 (m, 2H), 4.21–4.17 (m, 1H), 3.68 (s, 3H), 3.19 (A of AB, 1H, J=6.0, 14.0 Hz), 3.00 (B of AB, 1H, J=7.5, 14.0 Hz), 2.79–2.74 (m, 2H), 2.64–2.60 (M, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.8, 173.0, 155.8, 143.7, 141.3, 136.0, 129.2, 128.7, 127.7, 127.1, 127.0, 125.0, 120.0, 66.9, 60.5, 51.9, 47.1, 37.3, 35.0, 27.5. HRMS (M+H$^+$) calcd for $C_{28}H_{28}NO_5$ 458.1962, found 458.1938.

4.3. Scheme 3 experimentals

4.3.1. Phenylmethyl (4*S*)-4-(carboxy-*t*-butyl)-amino-3-oxo-pentanoate (11). Boc-L-alanine **8b** (176 mg, 0.93 mmol) was dissolved in 10 mL anhydrous THF in a 25 mL round-bottomed flask and 154 mg (0.95 mmol) CDI added while stirring. After being allowed to stir for 15 min, the acyl imidazole was transferred to a 100 mL flask containing a solution of monobenzyl malonate (722 mg, 3.72 mmol) in 30 mL anhydrous THF to which 1.86 mL (1.86 mmol) of a 1 M solution of dibutylmagnesium was

added at 0°C and warmed to room temperature (solution is colorless and clear). The reaction was monitored by TLC and stirred for 24 h before quenching in 30 mL sat. aq. NH_4Cl solution and extracting three times with 20 mL Et_2O. The combined organics were dried with $MgSO_4$ and concentrated before chromatographing on silica with 15% EtOAc in hexanes to yield 208 mg (70%) **11** as a colorless oil. ^1H NMR (360 MHz, $CDCl_3$) δ 7.38–7.31 (m, 5H), 5.18 (s, 2H), 5.08 (s, 1H), 4.36 (m, 1H), 3.66–3.56 (m, 2H), 1.44 (s, 9H), 1.33 (d, 3H, J=7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.4, 166.4, 155.5, 135.0, 128.6, 128.4, 128.3, 79.8, 67.2, 55.4, 45.7, 28.2, 16.8. HRMS ($M+Na^+$) calcd for $C_{17}H_{23}NO_5$ 344.1468, found 344.1464.

4.3.2. Phenylmethyl (5*S*)-5-(carboxy-*t*-butyl)-amino-4-oxo-hexanoate (12). A 50 mL round-bottomed flask was charged with 30 mL anhydrous CH_2Cl_2 and 375 μL (4.67 mmol) methylene iodide. The solution was cooled to 0°C and 3.11 mL (3.11 mmol) of a 1 M solution of diethylzinc in hexanes was slowly added. The ice bath was removed and a white precipitate formed rapidly. After stirring 2 min, 200 mg (0.62 mmol) of **11** dissolved in 5 mL CH_2Cl_2 was added and the reaction was monitored by TLC. The product spot appeared at a slightly higher R_f than starting material and was best visualized by staining the TLC plates with anisaldehyde. The reaction was complete after 30 min and was washed with 25 mL sat. aq. NH_4Cl solution before drying with $MgSO_4$ and concentrating. Flash chromatography on silica using 15% EtOAc in hexane yields 164 mg (79%) of **12** as a colorless oil. ^1H NMR (360 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 5.18 (m, 1H), 5.11 (s, 2H), 4.33 (m, 1H), 2.92–2.62 (m, 4H), 1.44 (s, 9H), 1.33 (d, 3H, J=7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.9, 172.3, 155.5, 135.7, 128.5, 128.3, 128.2, 79.8, 66.5, 55.0, 33.6, 28.3, 27.8, 17.6. HRMS ($M+Na^+$) calcd for $C_{18}H_{25}NO_5Na$ 358.1625, found 358.1599.

4.3.3. *N*-((1*S*)-1-Carbomethoxy-2-phenylethyl) (5*S*)-5-(carboxy-*t*-butyl)-amino-4-oxo-hexanoamide (14). Into a 10 mL round-bottomed flask containing 90 mg (0.26 mmol) **12** dissolved in 4 mL abs. EtOH was added 30 mg 10% Pd(C). The reaction vessel was stoppered and thoroughly flushed with nitrogen. The vessel was charged with hydrogen and the solution stirred for 10 min. After checking by TLC to ensure starting material was consumed, then reaction was filtered and concentrated to give 65 mg (99%) of a white crystalline solid. The dry solid was dissolved in 4 mL anhydrous DMF and to this solution was added 53 mg (0.27 mmol) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 37 mg (0.27 mmol) 1-hydroxybenzotriazole hydrate (HOBt), 60 mg (0.27 mmol) L-phenylalanine methyl ester hydrochloride, and 37 μl (0.27 mmol) triethylamine. The reaction was stirred overnight and then 10 mL sat. aq. NH_4Cl solution was added and the reaction was extracted with 2×20 mL EtOAc. The organic portion was washed with 15 mL sat. $NaHCO_3$ and 2×15 mL H_2O before drying with $MgSO_4$ and concentrating. Flash chromatography on silica using 40% EtOAc in hexanes yielded 99 mg (89%) **14** as a white solid; mp 89–90°C. ^1H NMR (360 MHz, $CDCl_3$) δ 7.31–7.21 (m, 3H), 7.11–7.09 (m, 2H), 6.12 (d, 1H, J=6.4 Hz), 5.25 (m 1H), 4.83 (q, 1H, J=5.8 Hz), 4.29 (m, 1H), 3.70 (s, 3H), 3.14–3.00 (m, 2H), 2.91–2.71 (m, 2H), 2.50–2.41 (m, 2H), 1.43 (s, 9H), 1.32 (d, 3H, J=7.16 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 208.5, 171.9, 171.0, 155.0, 135.8, 129.2, 128.5, 127.1, 79.9, 55.0, 53.1, 52.2, 37.8, 33.8, 29.4, 28.3, 17.6. HRMS ($M+Na^+$) calcd for $C_{21}H_{30}N_2O_6Na$ 429.1996, found 429.2010.

Acknowledgements

This research was funded by a grant from the National Institutes of Health (GM60967-01). C. R. T. acknowledges pre-doctoral support from Merck Pharmaceutical Research. Charles W. Ross, III, with Merck Pharmaceutical Research, provided HRMS data.

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