JOC*Article*

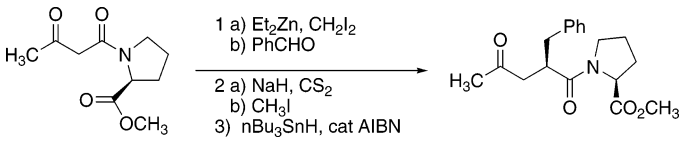
Stereocontrolled Formation of Ketomethylene Isosteres through Tandem Chain Extension Reactions

Weimin Lin,[†] Nancy Tryder,[†] Fan Su,[†] Charles K. Zercher,*[,†] Jerry P. Jasinski,[‡] and Ray J. Butcher[§]

Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824, Department of Chemistry, Keene State College, 229 Main Street, Keene, New Hampshire 03435, and Department of Chemistry, Howard University, 2400 Sixth Street, Washington, D.C. 20059

ckz@cisunix.unh.edu

Received June 8, 2006

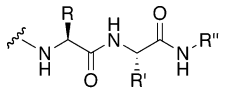


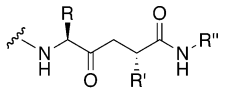
A zinc-mediated chain extension reaction is the key step in the preparation of γ-keto amides derived from amino acids. The use of tandem reaction sequences, in which the intermediate zinc enolate is trapped with electrophilic reagents, results in the incorporation of α-substituents, which mimic the side chains found in natural amino acid systems. Use of the chiral amino acid L-proline as a stereo-directing element provides a diastereoselective route to various ketomethylene isosteres.

Introduction

Isosteric replacement strategies are central to the development of many drug candidates. Specifically, the replacement of peptide bonds with non-hydrolyzable peptide isosteres has been used to provide substances resistant to the metabolic proteases. The design of a non-hydrolyzable peptide isostere that maintains active-site recognition features constitutes a recurring theme in protease inhibition. A variety of functional groups have been used to mimic the peptide bond, including hydroxyethylene,[1] (*E*)-alkenes,[2] silanols,[3] and dihydroxyethylene.[4]

The ketomethylene (**1**) unit has been utilized for the inhibition of a wide variety of enzymatic systems, including aminopeptidase,[5] angiotensin converting enzyme (ACE),[6] and others.[7] The appearance of ketomethylene isosteres in a naturally occurring protease inhibitor[8] further attests to the suitability of this strategy. The synthetic methodology developed in this study for ketomethylene isostere formation has potential ramifications in many therapeutic arenas.


peptide backbone


1

Generation of peptide mimics frequently requires lengthy and resource-intensive synthetic sequences. The desire for stereocontrolled incorporation of the α side chain complicates the synthetic issues even further. A host of methods[5−7,9] for the preparation of ketomethylene isosteric replacements have been

[†] University of New Hampshire.
[‡] Keene State College.
[§] Howard University.

(1) (a) Benedetti, F.; Berti, F.; Norbedo, S. *J. Org. Chem.* **2002**, *67*, 8635. (b) Kath, J. C.; DiRico, A. P.; Gladue, R. P.; Martin, W. H.; McElroy, E. B.; Stock, I. A.; Tylaska, L. A.; Zheng, D. *Bioorg. Med. Chem. Lett.* **2004**, *9*, 2163. (c) Tao, J.; Hoffman, R. V. *J. Org. Chem.* **1997**, *62*, 6240.

(2) (a) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088. (b) Oishi, S.; Kamano, T.; Niida, A.; Odagaki, Y.; Hamanaka, N.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Fujii, N. *J. Org. Chem.* **2002**, *67*, 6162.

(3) (a) Kim, J.; Sieburth, S. M. *J. Org. Chem.* **2004**, *69*, 3008. (b) Kim, J.; Glekas, A.; Sieburth, S. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3625.

(4) (a) Benedetti, F.; Magnan, M.; Miertus, S.; Norbedo, S.; Parat, D.; Tossi, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3027. (b) Atsuumi, S.; Ikeura, C.; Honma, T.; Morishima, H. *Chem. Pharm. Bull.* **1994**, *42*, 2164.

(5) (a) Harbeson, S. L.; Rich, D. H. *J. Med. Chem.* **1989**, *32*, 1378−1392. (b) Mansour, T. *Synth. Commun.* **1989**, *19*, 659−665.

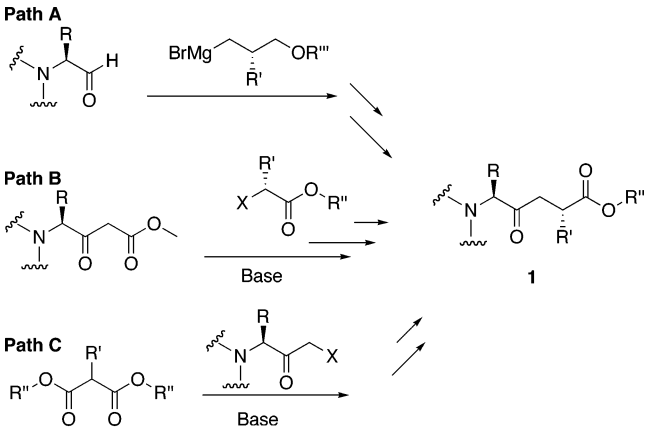
(6) Almquist, R. G.; Chao, W.-R.; Judd, A. K.; Mitoma, C.; Rossi, D. J.; Panesovich, R. E.; Matthews, R. J. *J. Med. Chem.* **1988**, *31*, 561.

(7) (a) Angelastro, M. R.; Marquart, A. L.; Mehdi, S.; Koehl, J. R.; Vaz, R. J.; Bey, P.; Peet, N. P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 139. (b) Ettouati, L.; Casimir, J. R.; Raynaud, I.; Trescol-Biemont, M.-C.; Carrupt, P.-A.; Gerlier, D.; Rabourdin-Combe, C.; Testa, B.; Paris, J. *Protein Pept. Lett.* **1998**, *5*, 221. (c) Marshall, G. R.; Toth, M. V. U.S. Patent 320,742, 1992. (d) Jones, D. M.; Atrash, B.; Teger-Nilsson, A.-C.; Gyzander, E.; Deinum, J.; Szelke, M. *Lett. Pept. Sci.* **1995**, *2*, 147. (e) Jones, D. M.; Atrash, B.; Ryder, H.; Geger-Nilsson, A.-C.; Gyzander, E.; Szelke, M. *J. Enzyme Inhib.* **1995**, *9*, 43.

(8) Umezawa, H.; Aoyagi, T.; Ohuchi, S.; Okuyama, A.; Suda, H.; Takita, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1983**, *36*, 1572.

10.1021/jo061184o CCC: $33.50
Published on Web 09/23/2006

SCHEME 1



reported. Common approaches (Scheme 1) to the ketomethylene group include nucleophilic attack on easily epimerized amino acid-derived aldehydes (Path A). Poor diastereoselectivity is often observed in the formation of the γ-hydroxy acid, and reoxidation can be troublesome. Furthermore, any α-substituent must be incorporated through a chiral Grignard agent, which limits side chain options to Grignard compatible functionality. Other common methods for the generation of γ-keto ester functionality involve enolate displacement of a bromide (or similar leaving group) from an α-bromocarbonyl (Path B). One such approach utilizes an electrophilic ester that is reacted with the salt of an amino acid-derived β-keto ester. Displacement has been reported with optically active substrates, which results in the generation of scalemic peptide isosteres.[10] The α side chains that can be incorporated through this approach are limited to those present in chiral α-hydroxy acids. A variation on this theme (Path C) uses a malonate anion to effect displacement of an amino acid-derived bromomethyl ketone. Alkylation and decarboxylation provide access to α-substituted systems, although control of stereochemistry is not possible.[11]

While the examples described above are representative of the methods that have been successfully applied to the preparation of ketomethylene-containing targets, the availability of a simple and efficient method that will facilitate the conversion of β-keto esters into the γ-keto ester targets could be tremendously useful. Of additional benefit would be a method that is flexible enough to allow the diverse incorporation of side-chain functionality. Successful development of this flexible methodology could contribute to a wide range of therapeutic targets.

We have reported that a zinc carbenoid-mediated chain extension reaction can be used to prepare di- and tripeptide mimics from amino acid-derived β-keto esters.[12] In this approach, a suitably protected amino acid was converted to a β-keto ester through application of the Masamune procedure.[13] Preparation of the β-keto ester was followed by exposure to ethyl(iodomethyl)zinc, which resulted in formation of the γ-keto ester (Scheme 2). A variety of amine-protecting groups, such as Boc, Cbz, Fmoc, and benzoyl (Bz), are tolerated with these conditions. Furthermore, a variety of amino acid starting materials, including lysine, aspartic acid, asparagine, and amino acids with the hydrocarbon side chains, have been chain-extended successfully. The efficiency of the reaction was not dependent upon the starting amino acid, and no epimerization of the amino acid's stereocenters was observed in the zinc-mediated chain extension reaction.

SCHEME 2

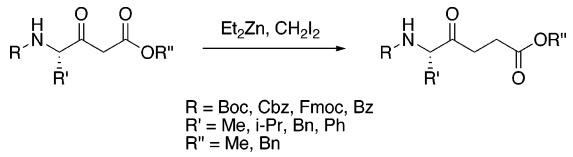
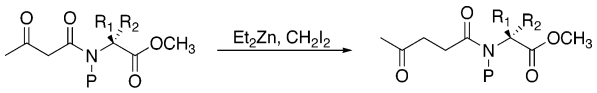


TABLE 1. Preparation of γ-Keto Amides



substrate	P	R_1	R2	product	yield (%)
2a	Cbz	H	H	3a	43
2b	H	Bn	H	3b	74
2c	H	*i*-Bu	H	3c	65
2d	H	Me	Me	3d	74
2e	H	$-(CH_2)_5-$		3e	83
2f	Bn	H	H	3f	36
2g	H	Ph	H	3g	54

The facile preparation of the γ-keto ester was satisfying, since the product contained the essential components of a dipeptide mimic in which a ketomethylene isostere was substituted for the peptide bond. We were interested in determining whether amino acid-derived β-keto amides were capable of chain extension through application of similar reaction conditions. Furthermore, we were interested in identifying a strategy by which to incorporate an α-substituent, which could serve to mimic the amino acid's side chain and could better mimic the peptide skeleton. Studies are reported below in which amino acid-derived β-keto amides are converted to the corresponding γ-keto amides. Incorporation of the side chains is accomplished through application of a tandem chain extension−aldol reaction and tandem chain extension−homoenolate generation reaction.

Results and Discussion

Diketene was reacted with various N-protected and -unprotected methyl esters of amino acids in the presence of sodium bicarbonate or pyridine to generate the corresponding β-keto amide substrates **2** (Table 1). Conditions reported earlier for chain extension of amino acid-derived β-keto esters were utilized for the formation of γ-keto amides **3**. A variety of amino acids were studied, although the study was limited to glycine and

(9) (a) Blakskjr, P.; Hoj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc*. **2003**, *125*, 4030. (b) Hoffman, R. V.; Kim, H.-O. *Tetrahedron Lett.* **1992**, *33*, 3579. (c) Dominguez, M. J.; Gonzales-Muniz, R.; Garcia-Lopez, M. T. *Tetrahedron* **1992**, *48*, 2761. (d) Szelke, M.; Jones, D. M.; Hallett, A. Eur. Pat. Appl. EP 45,665; *Chem. Abstr*. **1982**, *97*, 39405. (e) Garcia-Lopez, M. T.; Gonzales-Muniz, R.; Harto, J. R. *Tetrahedron Lett.* **1988**, *19*, 1577. (f) Dragovich, P. S.; Prins, T. J.; Zhou, R.; Webber, S. E.; Marakovits, J. T.; Fuhrman, S. A.; Patick, A. K.; Matthews, D. A.; Lee, C. A.; Ford, C. E.; Burke, B. J.; Rejto, P. A.; Hendrickson, T. F.; Tuntland, T.; Brown, E. L.; Meador, J. W., III.; Ferre, R. A.; Harr, J. E. V.; Kosa, M. B.; Worland, S. T. *J. Med. Chem*. **1999**, *42*, 1213. (g) Gomez-Monterrey, I.; Gonzalez Muniz, R.; Perez-Martin, C.; Lopez de Ceballos, M.; Del Rio, J.; Garcia-Lopez, M. T. *Arch. Pharm.* **1992**, *325*, 261.

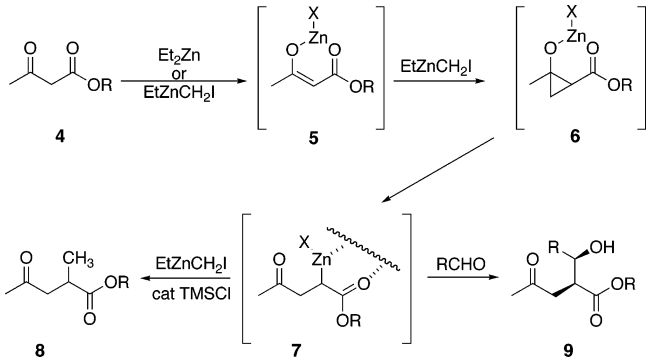
(10) Hoffman, R. V.; Kim, H.-O. *J. Org. Chem*. **1995**, *60*, 5107.

(11) Garcia-Lopez, M. T.; Gonzalez-Muniz, R.; Hartoa, J. R.; Gomez-Monterrey, I.; Perez, C.; De Ceballos, M. L.; Lopez, E.; Del Rio, J. *Arch. Pharm.* **1992**, *325*, 3.

(12) Theberge, C. R.; Zercher, C. K. *Tetrahedron* **2003**, *59*, 1521.

(13) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 72.

SCHEME 3



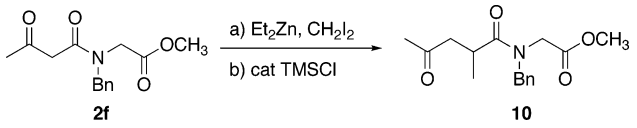
amino acids with hydrocarbon side chains. The effective chain extension of both secondary and tertiary β-keto amides was consistent with our previous report on chain extension of β-keto amides.[14] Poor yields of the isolated product were achieved with unprotected glycine; however, the incorporation of a benzyl group on the amide nitrogen provided access to modest yields of the glycine derivative (**3f**). If the nitrogen was protected with carbamate functionality (Cbz), the chain extension reaction appeared to proceed efficiently; however, the isolated yield of the purified γ-keto amide (**3a**) was diminished by the hydrolytic instability of the imide functionality. Therefore, the simple chain extension reactions were typically performed using secondary amides.

Efficient mimicry of the peptide backbone must include appropriately positioned side chains, preferably side chains with functionality and stereochemical orientation identical to those found in the natural amino acids. All of the substrates reported above, as well as the amino acid-derived β-keto esters reported in our earlier communication, lack this desired functionality at the amide or ester α-carbon. We have reported previously two tandem reaction strategies in which the intermediate formed in the chain extension is functionalized at the α-carbon through treatment with appropriate electrophilic reagents (Scheme 3). The use of the intermediate's nucleophilic character allows selective functionalization at the least acidic site in the molecule. We undertook an investigation of these tandem reaction strategies for the functionalization of the amino acid-derived ketomethylene skeleton.

Incorporation of an α-methyl substituent in γ-keto esters and amides is possible through treatment of the zinc enolate equivalent with excess carbenoid and catalytic TMSCl.[15] This method of incorporating a methyl group adjacent to the amide carbonyl would appear to be suitable for mimicking the methyl side chain found in alanine. The first attempt to incorporate the α-methyl group was performed on a leucine-derived secondary amide **2c**. All efforts to effect methylation of the α-carbon resulted in isolation of the unsubstituted γ-keto amide **3c**, presumably due to protonation of the intermediate zinc enolate by the secondary amide's NH. Quenching of the intermediate's enolate equivalent by an amide proton was reported in earlier studies.[15]

An alternate achiral β-keto amide (**2f**), derived from *N*-benzyl glycine, was selected due to the absence of the modestly acidic NH. The substrate was rigorously dried by heating under high vacuum prior to its addition to 4 equiv of the zinc carbenoid.

SCHEME 4

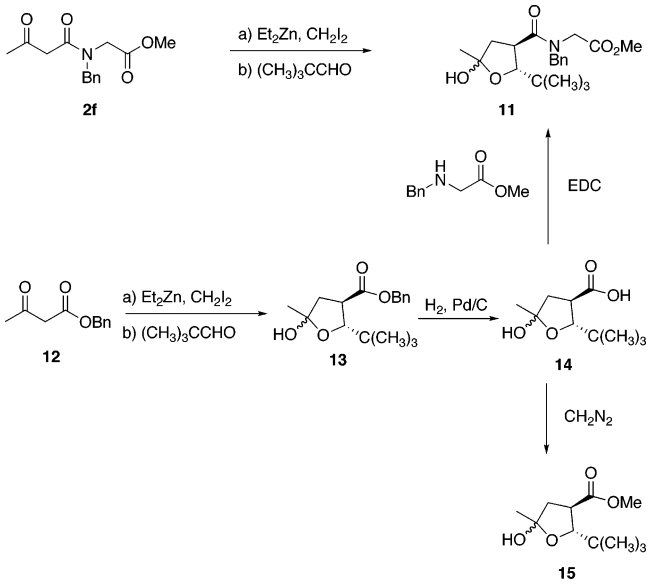


Upon addition of catalytic TMSCl, the purified α-methylated product **10** was isolated in 22% yield. The low yield was not unexpected, since the yield for chain extension of this glycine-derived substrate was only 36%.

An alternative, and potentially higher yielding, method for the incorporation of the side chain involved a tandem chain extension−zinc aldol reaction.[16] We had reported earlier that β-keto esters could be chain-extended and treated with various aldehydes to provide good yields of α-substituted γ-keto esters. In most cases, the aldol reaction was syn selective, with a typical syn:anti ratio greater than 10:1; however, only a single β-keto amide starting material was included in that study. The analysis of products derived from tandem chain extension−aldol reactions is complicated by hemiacetal formation of both the syn and anti isomers. The use of derivatized chiral amino acids in tandem chain extension−aldol reactions presents additional complexity in the analysis due to diastereofacial-selectivity issues and the appearance of rotameric forms. To simplify the analysis, the reaction was first performed on a starting material derived from an achiral amino acid. The β-keto amide **2d**, derived from dimethyl isobutyric acid, upon chain extension and exposure to benzaldehyde, provided only chain-extended material **3d**. Once again, this result was not unexpected due to the presence of the amide proton.

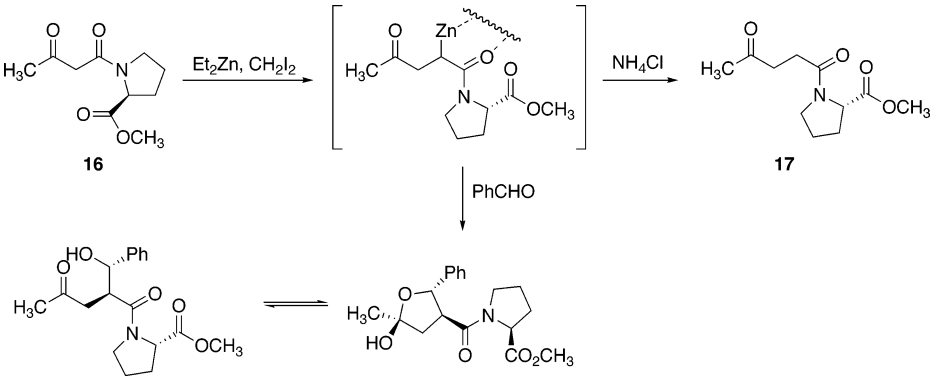
The β-keto amide **2f**, derived from *N*-benzyl glycine methyl ester, was studied in a tandem reaction sequence in which the enolate was reacted with trimethylacetaldehyde. Chromatographic purification provided a single product **11**; however, the identity of the material, in particular the stereochemical relationships, could not be assigned with confidence. Analysis by ^{1}H NMR was complicated due to the presence of amide rotamers and the presumed existence of both open and closed (hemiacetal) forms of the product. Analysis via ^{13}C NMR clearly illustrated the existence of the acyclic form with a ketone carbonyl signal

SCHEME 5



(14) Hilgenkamp, R.; Zercher, C. K. *Tetrahedron* **2001**, *57*, 8793.
(15) Hilgenkamp, R.; Zercher, C. K. *Org. Lett.* **2001**, *3*, 3037.

SCHEME 6



above 200 ppm and the cyclic forms (hemiacetals) with resonances ranging between 100 and 110 ppm for the acetal carbon.

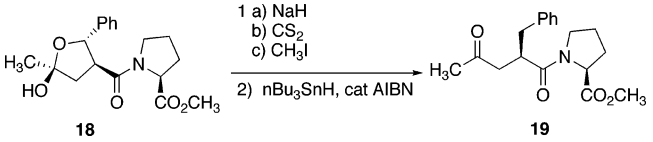
An independent synthesis of the syn isomer **11** was undertaken to confirm the identity and stereochemistry of the product. Benzyl acetoacetate **12** was converted to the hemiacetal **13** through the tandem chain extension−aldol protocol.[16] Acid **14** was obtained via hydrogenolysis and immediately coupled with *N*-benzyl glycine methyl ester via the action of EDC. Product **11** was identical to the major component in the tandem chain extension−aldol reaction performed earlier (Scheme 5), thereby confirming the identical diastereoselectivity of the tandem chain extension−aldol reaction on β-keto amide **2f**. When acid **14** was treated with diazomethane, the known *syn*-aldol product **15**[16] was generated, confirming the syn stereochemical assignment of **11**. It should be noted that *syn*-aldol selectivity is required for the formation of threonine mimics.

While the tandem reaction procedures illustrated in Schemes 4 and 5 provided access to modified amino acid skeletons, the control of absolute stereochemistry had not been explored. The methyl ester of L-proline was reacted with diketene to provide a β-keto amide **16**. The chain extension reaction proceeded cleanly to provide γ-keto amide **17**. Exposure of **16** to the zinc carbenoid followed by addition of benzaldehyde resulted in a good yield of a single aldol product **18** (Scheme 6). Although the existence of rotameric forms and the presence of both acyclic and cyclic (hemiacetal) isomeric forms made analysis of the crude reaction mixture difficult, generation of an X-ray quality crystal allowed the assignment of the stereochemistry of the major reaction product. The aldol reaction was, as expected, syn selective. The enolate facial selectivity observed in the reaction was influenced by the L-proline, with the newly incorporated α-stereocenter consistent with the natural stereochemistry found in L-amino acids.

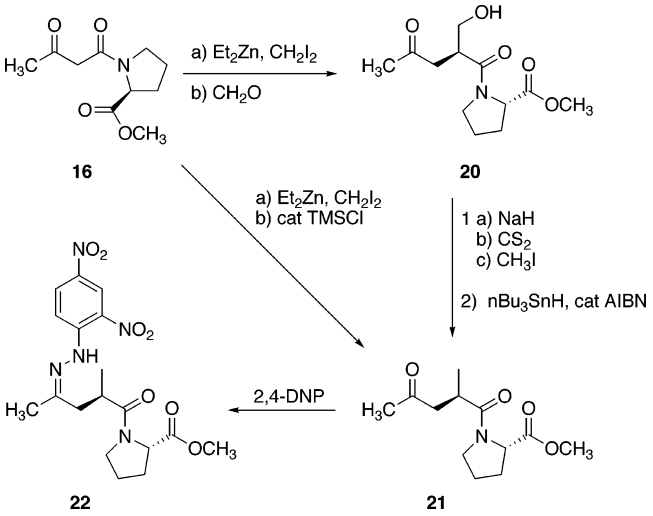
The aldol product **18** could be manipulated to provide access to side chains found in the natural amino acids. Formation of the xanthate could be accomplished through opening the hemiacetal. Reductive cleavage of the xanthate resulted in a phenylalanine mimic (Scheme 7).

A serine mimic **20** was formed in the reaction of **16** with formaldehyde. Once again, the enolate facial selectivity was outstanding. The hydroxymethyl side chain, which prefers the acyclic form, could be converted to the xanthate and reduced with tributyltin hydride to provide the α-methylated γ-keto amide (alanine mimic) **21** (Scheme 8). The stereoselectivity of this aldol reaction was established through comparison of **21** to an identical material generated through the homoenolate strategy described below.

SCHEME 7



SCHEME 8



An alternative approach to the alanine mimic through chain extension and treatment with catalytic TMSCl was explored. Protonation of the intermediate homoenolate provided the α-methylated γ-keto amide **21**. Diastereoselectivity of this methylation reaction was estimated as >92:8 from ^{1}H NMR integration. The relative stereochemistry was established through X-ray crystallographic analysis of the 2,4-dinitrophenylhydrazone derivative **22**. Once again, the L-proline stereocenter influenced formation of natural (L)-stereochemistry at the α-carbon. The spectral data for **21** generated via the tandem chain extension−aldol sequence was identical to that generated via the homoenolate.

In conclusion, we have demonstrated that zinc carbenoid-mediated chain extension reactions can be performed on amino acid-derived β-keto amides. The products of these reactions are γ-keto amides, which appear suitable to serve as ketomethylene

(16) Lai, S.-J.; Zercher, C. K.; Jasinski, J. P.; Reid, S. N.; Staples, R. J. *Org. Lett.* **2001**, *3*, 4169.

isosteric replacements for peptide bonds. The use of tandem reaction processes facilitates the incorporation of side chains into these mimics. The chain extension−aldol reaction proceeds with threonine-like stereoselectivity. The alcohol functionality can be deoxygenated to provide hydrocarbon side chains. Methylation can be induced through the intermediacy of an intermediate homoenolate, which provides direct access to alanine analogues. Use of L-proline-derived β-keto amides offers efficient diastereocontrolled formation of L-amino acid mimics. Studies involving more complex starting materials are underway in our laboratory, as well as studies that target specific proteases through ketomethylene isostere formation.

Experimental Section

2-(5-Hydroxy-5-methyl-2-phenyltetrahydrofuran-3-carbonyl)-cyclopentanecarboxylic Acid Methyl Ester (18). A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 10 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C, and methylene iodide (0.20 mL, 2.5 mmol) was added slowly by syringe. After the solution was stirred for 10 min, compound **16** (0.22 g, 1.0 mmol, in 2 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 min, at which time freshly distilled benzaldehyde (0.13 g, 1.2 mmol) was added into the reaction mixture by syringe. After TLC analysis (hexane/ethyl acetate, 1.5:1; $R_f = 0.20$) indicated the chain extension intermediate was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (10 mL). The mixture was extracted with diethyl ether (2 × 15 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexane/ethyl acetate, 1:1; $R_f = 0.25$) to yield 0.23 g (70%) of compound **18** as white crystals (mp 113−115 °C) in which one major hemiacetal form was present. $[\alpha]^{25}_D$ −11.6° (*c* 0.011 g/mL, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.26 (m, 5H), 6.65 (s, 1H,), 5.18 (d, 1H, $J = 5.0$ Hz), 4.56 (dd, 1H, $J = 3.5$, 8.6 Hz), 3.80 (s, 3H), 3.38−3.23 (m, 3H), 2.31−1.84 (m, 6H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 171.9, 142.0, 128.5, 127.8, 125.4, 105.3, 83.2, 58.8, 52.2, 51.0, 47.6, 41.6, 28.9, 24.9, 24.3. The presence of the open chain form as a minor constituent is confirmed by the ^{13}C resonance of 207.7. IR (neat, cm^{-1}): 3400 (b, OH), 2956, 1744, 1640, 1448.

1-(2-Benzyl-4-oxopentanoyl)-pyrrolidine-2-carboxylic Acid Methyl Ester (19). A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with sodium hydride (24 mg, 0.6 mmol, 60% in the mineral oil). Hexanes (2 mL) were added to the flask to wash the sodium hydride. The hexane was removed by syringe, and then tetrahydrofuran (4 mL) was added by syringe. The solution was cooled to 0 °C, and carbon disulfide (76 mg, 1.0 mmol) was added by syringe. After the solution was stirred for 5 min, compound **18** (0.10 g, 0.3 mmol, in 1 mL of tetrahydrofuran) was added by syringe, followed by methyl iodide (0.14 mg, 1.0 mmol). After TLC analysis (hexane/ethyl acetate, 1:1; $R_f = 0.25$) indicated the starting material **18** was consumed, the solution was quenched with saturated aqueous ammonium chloride (3 mL). The solution was extracted with diethyl ether (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexane/ethyl acetate, 1.5:1; $R_f = 0.20$) to yield 96 mg (74%) of the xanthate as a yellow oily mixture of two rotamers in a 3.3:1 ratio. $[\alpha]^{25}_D$ +15° (*c* 0.004 g/mL, $CHCl_3$). Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 6.59 (d, 1H, $J = 9.0$ Hz), 4.31 (dd, 1H, $J = 4.4$, 8.4 Hz), 3.77−3.64 (m, 2H), 3.64 (s, 3H), 3.22 (dd, 1H, $J = 10.3$, 18.3 Hz), 2.92 (m, 1H), 2.79 (dd, 1H, $J = 2.9$, 18.3 Hz), 2.55 (s, 3H), 2.14 (s, 3H), 2.06 (m, 1H), 1.88−1.73 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 207.2, 172.2, 169.8, 137.0, 128.5, 128.4, 127.4, 84.1, 59.2, 51.9, 47.0, 45.4, 43.6, 30.1, 29.2, 24.8, 19.2. Resonances observed for the minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (d, 1H, $J = 10.0$ Hz), 3.84 (d, 1H, $J = 8.6$ Hz), 3.77 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 205.7, 172.3, 169.7, 137.4, 128.5, 126.8, 85.0, 59.1, 52.3, 46.1, 45.8, 43.5, 30.6, 30.2, 22.1, 19.2. IR (neat, cm^{-1}): 2954−2852, 1740, 1715, 1640, 1436, 1202. HRMS (ESI) Calcd for $[M^+ + H]$): 424.1247; Found: 424.1255.

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). The xanthate (0.16 g, 0.4 mmol), tributyltin hydride (0.16 mL, 0.6 mmol), and AIBN (10 mg, 0.06 mmol) were added sequentially to the flask. The solution was heated to 80 °C for 8 h. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1:1; $R_f = 0.11$) to give 88 mg of compound **19**. $[\alpha]^{25}_D$ +3.8° (*c* 0.002 g/mL, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.18 (m, 5H), 4.46 (dd, 1H, $J = 4.7$, 8.9 Hz), 3.81 (m, 1H), 3.73 (s, 3H), 3.40 (m, 1H), 3.20 (m, 1H), 3.12−3.00 (m, 2H), 2.59 (dd, 1H, $J = 8.8$, 13.7 Hz), 2.38 (dd, 1H, $J = 3.2$, 18.0 Hz), 2.18 (m, 1H), 2.06 (s, 3H), 2.06−1.92 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 173.4, 172.7, 138.7, 129.1, 128.4, 126.4, 58.7, 52.0, 46.8, 45.1, 40.6, 37.7, 29.9, 29.1, 24.8. IR (neat, cm^{-1}): 2923−2851, 1744, 1713, 1634, 1436, 1365. HRMS (ESI) Calcd for $[M^+ + Na]$: 340.1519; Found: 340.1517.

1-(2-Hydroxymethyl-4-oxopentanoyl)-pyrrolidine-2-carboxylic Acid Methyl Ester (20). A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 35 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 15.0 mL, 15.0 mmol). The solution was cooled to 0 °C, and methylene iodide (1.20 mL, 15.0 mmol) was added slowly by syringe. After the solution was stirred for 10 min, compound **16** (0.64 g, 3.0 mmol, in 3 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 min. Paraformaldehyde (0.5 g) was placed in a dry one-necked round-bottomed flask, which was capped with a rubber septum. One end of a wide-bore cannula was inserted through the septum in the flask that contained paraformaldehyde, and the other end of the cannula was inserted through the septum in the flask that contained the zinc reagent. The paraformaldehyde flask was heated with a heat gun to induce formation of formaldehyde, which was bubbled into the zinc-carbenoid solution for 10 min. (*Caution*: Polymerization of the gaseous formaldehyde in the cannula, which can cause blockage of the cannula, must be avoided. Use of a tygon tube with barrels of disposable syringes at either end provides a suitable cannula for this purpose) After TLC analysis (hexane/ethyl acetate, 1.5:1; $R_f = 0.20$) indicated the chain extension intermediate was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (15 mL). The solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexane/ethyl acetate, 1:1; $R_f = 0.20$) to yield 0.57 g (74%) of compound **20** as a yellow oil with some minor hemiacetal forms present. $[\alpha]^{25}_D$ −25.3° (*c* 0.003 g/mL, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (dd, 1H, $J = 4.8$, 8.9 Hz), 3.88−3.84 (m, 2H), 3.72 (s, 3H), 3.68−3.66 (m, 2H), 3.28 (m, 1H), 3.20 (t, 1H, $J = 7.0$ Hz), 3.01 (dd, 1H, $J = 10.0$, 18.4 Hz), 2.48 (dd, 1H, $J = 3.7$, 18.4 Hz), 2.24 (m, 1H), 2.12 (s, 3H), 2.02−1.93 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 173.6, 173.3, 64.5, 58.8, 52.5, 47.3, 42.1, 41.2, 29.8, 29.0, 24.8. Minor hemiacetal forms: ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 172.6, 172.0, 105.0, 104.9, 69.5, 69.4, 25.1, 24.6. IR (neat, cm^{-1}): 3435 (b, OH), 2956−2852, 1743, 1714, 1624, 1447. HRMS (ESI) Calcd for $[M^+ + Na]$: 280.1155; Found: 280.1152.

1-(2-Methyl-4-oxopentanoyl)-pyrrolidine-2-carboxylic Acid Methyl Ester (21) (via Xanthate Formation and Reduction). A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with sodium hydride (48 mg, 1.2 mmol, 60% in the mineral oil). Hexanes (2 mL) were added to the flask to wash the sodium hydride. The hexane was removed by syringe, and then tetrahydrofuran (4 mL) was added by syringe. The solution was cooled to 0 °C, and carbon disulfide (0.15 g, 2.0 mmol) was added by syringe. After the solution was stirred for 5 min, compound **20** (0.26 g, 1.0 mmol, in 1 mL of THF) was added by syringe, followed by methyl iodide (0.21 g, 1.5 mmol). After TLC analysis (hexane/ethyl acetate, 1:1; $R_f = 0.20$) indicated the starting material **20** was consumed, the solution was quenched with saturated aqueous ammonium chloride (3 mL). The solution was extracted with diethyl ether (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexane/ethyl acetate, 1.5:1; $R_f = 0.2$) to yield 0.24 g (68%) of the xanthate as a yellow oil. $[\alpha]^{25}_D$ −2.0° (*c* 0.007 g/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (dd, 1H, $J = 7.3$, 10.7 Hz), 4.58 (dd, 1H, $J = 7.3$, 10.7 Hz), 4.46 (dd, 1H, $J = 4.6$, 8.6 Hz), 3.90 (m, 1H), 3.79 (m, 1H), 3.70 (s, 3H), 3.58 (m, 1H), 3.14 (dd, 1H, $J = 10.4$, 18.2 Hz), 2.60 (dd, 1H, $J = 3.3$, 18.2 Hz), 2.58 (s, 3H), 2.22 (m, 1H), 2.15 (s, 3H), 2.10−1.96 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 206.5, 172.4, 170.5, 72.9, 59.0, 52.2, 47.3, 42.8, 38.1, 29.9, 29.2, 24.9, 19.0. IR (neat, cm^{-1}): 2955−2850, 1743−1640, 1640, 1214, 1068. HRMS (ESI) Calcd for $[M^+ + H]$: 348.0934; Found: 348.0936.

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). The xanthate (35 mg, 0.1 mmol), tributyltin hydride (0.05 mL, 0.2 mmol), and AIBN (5 mg, 0.03 mmol) were added to the flask in the indicated order. Then the solution was heated to 80 °C for 8 h. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1; $R_f = 0.15$) to give 17 mg (70%) of compound **21** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (dd, 1H, $J = 4.6$, 8.7 Hz), 3.83−3.64 (m, 2H), 3.70 (s, 3H), 3.12−2.94 (m, 2H), 2.36 (dd, 1H, $J = 3.2$, 17.3 Hz), 2.12 (s, 3H), 2.25−1.93 (m, 4H), 1.15 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 174.5, 172.9, 58.5, 52.1, 47.2, 46.8, 33.1, 30.1, 29.1, 24.9, 16.7. IR (neat, cm^{-1}): 2957, 1746, 1645, 1434.

1-(2-Methyl-4-oxopentanoyl)-pyrrolidine-2-carboxylic Acid Methyl Ester (21) (via Homoenolate). A 100-mL round-bottomed flask was equipped with a stir bar and septum and was charged with 15 mL of methylene chloride and diethyl zinc (5.0 mL of a 1.0 M solution in hexane, 5.0 mmol) under a nitrogen atmosphere. The flask was immersed in an ice−water bath, and the solution was cooled to 0 °C. Methylene iodide (1.1 mL, 7.5 mmol) was added in one portion, and the solution was stirred for 10 min. β-Keto ester **16** (0.400 g, 1.9 mmol, dissolved in 5 mL of methylene chloride) was added to the white suspension, and the mixture was stirred for 40 min, at which time chlorotrimethylsilane (0.4 mL, 2.7 mmol) was added. The reaction was allowed to stir for 80 min, then quenched with the addition of 20 mL of saturated aqueous ammonium chloride. The mixture was extracted with diethyl ether, which was washed with brine and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated on a rotary evaporator. The residue was chromatographed on silica (hexane/ethyl acetate, 3:1; $R_f = 0.15$) to yield 0.187 g (39%) of compound **21** as a yellow oil. $[\alpha]_D^{25}$ −58.4° (*c* 0.125, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49−4.45 (dd, 1H, $J = 4.4$, 8.1 Hz), 3.84−3.64 (m, 2H), 3.71 (s, 3H), 3.14−3.02 (m, 2H), 2.12 (s, 3H), 2.42−1.94 (m, 4H), 1.15 (d, 3H, $J = 10$ Hz); ^{13}C NMR (125 MHz, $CHCl_3$) δ 208.1, 174.8, 173.2, 58.8, 52.3, 47.4, 47.0, 33.3, 30.3, 29.3, 25.1, 16.9; IR (neat, cm^{-1}) 2957, 1746, 1645, 1434.

2,4-Dinitrophenylhydrazone Derivative of 21 (22). Concentrated sulfuric acid (0.2 mL) was added to a test tube that contained 2,4-dinitrophenylhydrazine (119 mg, 0.6 mmol). Distilled water was added dropwise with swirling until the hydrazine reagent dissolved. To this warm solution was added 2 mL of 95% ethanol. The freshly prepared 2,4-DNP solution was added to a solution of **21** (120 mg in 2 mL of 95% ethanol, 0.5 mmol). The solution was allowed to sit at room temperature for 24 h, at which time crystallization was observed. The solution that contained the crystals was concentrated on a rotary evaporator, and the resulting solid orange residue dissolved in a mixture of EtOAc/$CHCl_3$ (approximately 15:1) over a steam bath. The clear orange solution was stored in a refrigerator (approximately 5 °C). Formation of crystals (clear prisms, mp = 164−165 °C) was observed within 24 h. $[\alpha]_D^{25}$ −60.7° (*c* 0.173, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 9.12 (s, 1H), 8.26−7.65 (m, 2H), 4.49−4.45 (dd, 1H, $J = 4.4$, 8.1 Hz), 3.84−3.64 (m, 2H), 3.71 (s, 3H), 3.14−3.02 (m, 2H), 2.12 (s, 3H), 2.42−1.94 (m, 4H), 1.15 (d, 3H, $J = 10$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 173.2, 156.8, 145.3, 137.5, 130.0, 124.0, 115.8, 59.3, 52.8, 47.1, 42.4, 35.2, 29.8, 25.0, 17.2; IR (neat, cm^{-1}) 3338, 1744, 1637, 1431. HRMS (ESI) Calcd for $[M^+ + H]$: 422.1676; Found: 422.1670.

Supporting Information Available: Experimental procedures for the preparation of **2a**−**g**, **3a**−**g**, **10**, **11**, **16**, and **17**. ^{1}H and ^{13}C NMR spectra of **2a**−**g**, **3a**−**g**, **10**, **11**, **16**, **17**, **18**, **19**, **21**, and **22**. Crystal structure data for **18** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061184O