Diastereoselective Synthesis of the Carbacephem Framework

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Received August 14, 1992

A short, versatile, and diastereoselective method of preparing carbacephems has been developed. The procedure involves as a key step the aldol condensation of a protected glycine compound with a suitably designed aldehyde. In this step, most of the carbon skeleton of the carbacephem is assembled, and the two stereocenters of the final bicyclic β-lactam are set. This step also provides well-placed and synthetically useful functionality for further elaboration into the desired target.

Introduction

As new β-lactam antibiotics are constantly being sought to meet the ongoing challenges of bacterial resistance to existing drugs, the most promising new class of these important compounds is the carbacephems. Although marked by potent antibacterial activity[1] and improved in vivo stability[1b,2] compared to cephalosporins, sufficiently concise methods of preparing carbacephems for pharmaceutical application have been elusive. Improvements are needed to reduce the number of synthetic steps in order to arrive at a commercially attractive synthesis.[3]

We sought to investigate approaches to building the carbacephem structure 1 that would accomplish this goal in fewer overall steps. The key intermediate in our approach is a β-hydroxy-α-amino acid 2. By carefully designing this intermediate, it may possess most of the carbon atoms needed to construct the bicyclic carbacephem nucleus. Additionally, this type of amino acid can also incorporate the functionality and stereochemistry needed for biological activity. Important features of carbacephems are the presence of an acylated amine functionality at C_7 and cis-β (*S,R*) stereochemistry at the C_6 and C_7 positions (Figure 1).

In previous studies,[4] we had shown that an enzymatic approach could be used to synthesize a wide variety of β-hydroxy-α-amino acids with the appropriate L-anti stereochemistry as well as functionality suitable for elaboration into β-lactams, including, potentially, carbacephems. After demonstrating the ability of enzyme-mediated synthesis to produce β-hydroxy-α-amino acids, we then sought to explore the downstream chemistry with racemic materials to establish that such amino acids could be ultimately converted to carbacephems. Since those initial enzymatic studies were performed on an analytical scale, it was necessary to synthesize by chemical means larger quantities of the amino acids to be used for the present studies. Here we report details of the synthesis of a carbacephem from a β-hydroxy-α-amino acid.

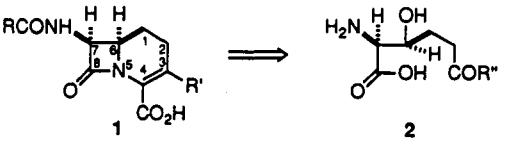

Figure 1.

Results and Discussion

The β-hydroxy-α-amino acid that we initially prepared was a protected form of DL-*anti* α-amino-β-hydroxyadipic acid (8). We were interested in this amino acid because it had six of the eight carbon atoms needed for the components of a carbacephem, and it has well-placed functional groups to allow subsequent synthetic manipulations. This amino acid may be prepared by an aldol condensation of a suitably protected glycine and an ester of succinic semialdehyde. Succinic semialdehyde methyl ester (4) had proven to be one of the best aldehyde substrates tested in our previous enzymatic work, and we therefore deemed it appropriate to begin our synthetic efforts by using this aldehyde, which was prepared by ozonolysis of methyl 4-pentenoate (3) (Scheme I).

For the glycine component of the reaction we chose the allyl ester of 4,5-diphenyl-1-oxazolin-2-one[5] ("Ox") protected glycine 7, which was prepared in good yield from cyclic carbonate 5 and tetramethylammonium glycinate to give Ox-glycine 6, followed by esterification[6] (Scheme II). Amino acid 8 was then prepared in 92% yield by aldol condensation of aldehyde 4 with the lithium enolate of 7.

Upon examination of the proton NMR of the crude product, only one diastereomer of 8 could be detected, although racemic. The aldol reaction therefore proceeded with a very high degree of diastereoselectivity. We attributed this selectivity to the presence of the Ox group, which had been seen previously in other aldol reactions in our laboratory to give modest (4:1) selectivity, favoring

(1) (a) Firestone, R. A.; Fahey, J. L.; Maciejewicz, N. S.; Patel, G. S.; Christensen, B. G. *J. Med. Chem.* **1977**, *20*, 551. (b) Blaszczak, L. C.; Brown, R. F.; Cook. G. K.; Hornback, W. J.; Hoying, R. C.; Indelicato, J. M.; Jordan, C. L.; Katner, A. S.; Kinnick, M. D.; McDonald, J. H., III; Morin, J. M., Jr.; Munroe, J. E.; Pasini, C. E. *J. Med. Chem.* **1990**, *33*, 1656. (c) Mochida, K.; Shiraki, C.; Yamasaki, M.; Hirata, T.; Sato, K.; Okachi, R. *J. Antibiot.* **1987**, *40*, 14.

(2) (a) Hirata, T.; Matsukuma, I.; Mochida, K.; Sato, K. *Program and Abstracts of the 27th Intersci. Conf. Antimicrob. Agents Chemother.* 1987; Abstract 1187. (b) Wiedemann, B. *Ibid.*; Abstract 1198. (c) Fontana, R.; Pelosi, R. *Ibid.*; Abstract 1199. (d) Gray, G.; Ramotar, K.; Krulicki, W.; Louie, T. J. *Ibid.*; Abstract 1200. (e) At least one carbacephem has lower chemical stability than the analogous cephalosporin. See: Narisada, M.; Yoshida, T.; Ohtani, M.; Ezumi, K.; Takasuka, M. *J. Med. Chem.* **1983**, *26*, 1577.

(3) (a) Bodurow, C. C.; Boyer, B. D.; Brennan, J.; Bunnell, C. A.; Burks, J. E.; Carr, M. A.; Doecke, C. W.; Eckrich, T. M.; Fisher, J. W.; Gardner, J. P.; Graves, B. J.; Hines, P.; Hoying, R. C.; Jackson, B. G.; Kinnick, M. D.; Kochert, C. D.; Lewis, J. S.; Luke, W. D.; Moore, L. L.; Morin, J. M., Jr.; Nist, R. L.; Prather, D. E.; Sparks, D. L.; Vladuchick, W. C. *Tetrahedron Lett.* **1989**, *30*, 2321. (b) Zmijewski, M. J., Jr.; Briggs, B. S.; Thompson, A. R.; Wright, I. G. *Tetrahedron Lett.* **1991**, *32*, 1621.

(4) Lotz, B. T.; Gasparski, C. M.; Peterson, K.; Miller, M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1107.

(5) (a) Sheehan, J. C.; Guziec, F. S., Jr.; *J. Am. Chem. Soc.* **1972**, *94*, 6561. (b) Sheehan, J. C.; Guziec, F. S., Jr.; *J. Org. Chem.* **1973**, *38*, 3034. For use of the Ox group in β-lactam syntheses, see refs 16a and 16c.

(6) Friedrich-Bochnitschek, S.; Waldmann, H.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 751.

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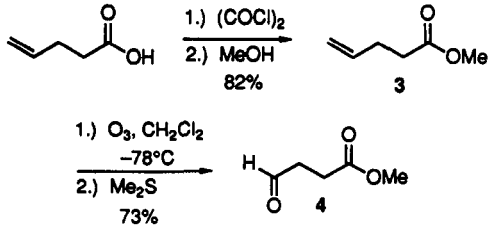
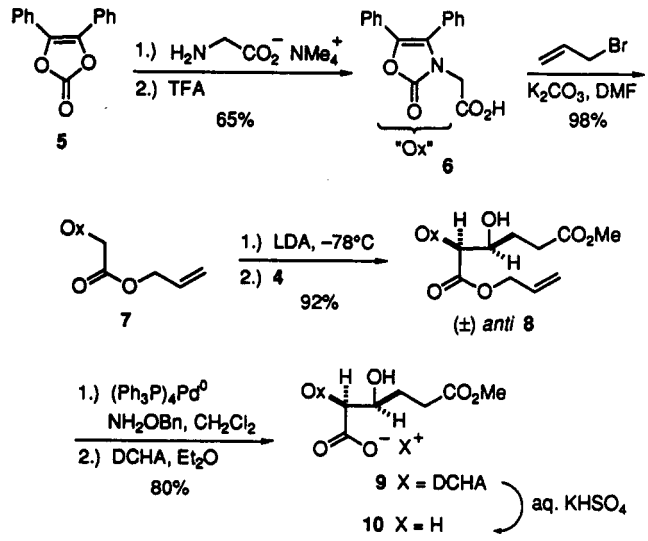
Scheme I



Scheme II



the anti isomer.[7] In contrast, other diprotecting groups, such as phthalimide, tend to favor syn products. The specific role of the Ox group is not certain, but unlike the phthalimide group, the Ox group is not planar. Instead, the phenyl rings are twisted out of the plane of the oxazolinone ring due to steric crowding. This apparently acts to direct the orientation of the aldehyde in the transition state, which is presumed to involve an *E*(O)-enolate in a Zimmerman–Traxler[8] chair in which the Ox group and aldehyde alkyl chain occupy equatorial positions (Figure 2).

Although our primary goal was to prepare carbacephems, it is important to note that intermediate compounds we prepared are of interest and value in their own right. β-Hydroxy-α-amino acids are found in many natural compounds[9] and also serve as synthetic intermediates leading to other types of organic structures.[10] Many methods of constructing these amino acids have been developed,[11] but most are lacking in some way, such as lack of versatility, lengthy procedures, or inability to

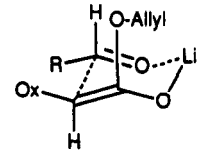
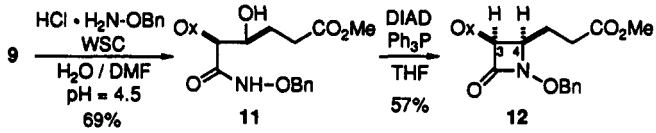


Figure 2.

Scheme III



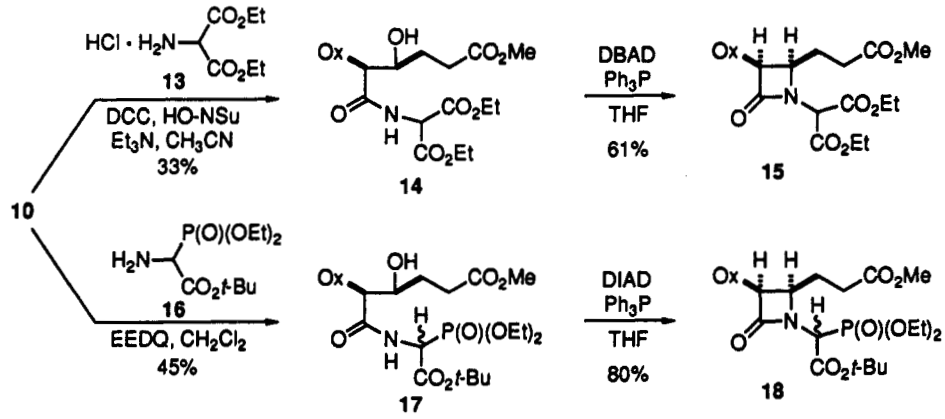
produce the anti stereochemistry. The chemistry presented in this paper represents a valuable addition to the inventory of available synthetic methods.

At this point in the synthesis, we were unable to determine which diastereomer of **8** had actually been favored in the aldol condensation, so a portion of the product was converted to a simple β-lactam in order to answer this question. The allyl ester was readily deprotected with catalytic palladium(0), using *O*-benzylhydroxylamine as allyl cation scavenger. The resulting crude free acid (**10**) was purified by conversion to its dicyclohexylammonium (DCHA) salt **9**, which was then precipitated from ether. The DCHA salt could optionally be reconverted, quantitatively, to pure **10** by treating the salt with a biphasic mixture of aqueous 5% $KHSO_4$ and ethyl acetate.[12] Although salt **9** was used initially for coupling reactions, its low solubility in most solvents made regeneration of free acid **10** advantageous.

Once deprotected amino acid **9** was obtained, a portion of the material was diverted for determination of the diastereochemical relationship at the α and β positions. A diagnostic method for making this determination is by conversion to a β-lactam and measuring in the NMR spectrum the coupling constants of the protons at the two stereocenters. Conversion to a β-lactam was a two-step process (Scheme III). As this was one of the earlier coupling experiments, salt **9** was employed rather than free acid **10**. The salt was coupled to *O*-benzylhydroxylamine hydrochloride with a water-soluble carbodiimide (WSC, 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide[13]) in aqueous *N*,*N*-dimethylformamide (DMF) at a pH of 4.5. The yield of hydroxamate **11** was 69% after chromatography. *O*-Benzylhydroxylamine was chosen for this coupling because the proton NMR spectrum of the corresponding β-lactam (**12**) would be free of overlapping signals in the region of interest, i.e., about 3.5–4.5 ppm, where the C_3 and C_4 protons would appear. This same coupling was also accomplished later with free acid **10** and either WSC or EEDQ[14] as coupling agent. Cyclization by a Mitsunobu reaction,[15] using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine, then afforded a 57% yield of β-lactam **12**. From this compound the stereochemical relationship of the ring substituents was determined by

(7) Jung, M.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 977.
(8) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(9) See, for example: (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757. (b) Teintze, M.; Hossain, M. B.; Barnes, C. L.; Leong, J.; Van der Helm, D. *Biochemistry* **1981**, *20*, 6446. (c) Kato, T.; Hinoo, H.; Terui, Y.; Kikuchi, J.; Shoji, J. *J. Antibiot.* **1988**, *61*, 719. (d) Wichmann, C. F.; Liesch, J. M.; Schwartz, R. E. *J. Antibiot.* **1989**, *62*, 168.
(10) For example, see: (a) Cooper, J.; Gallagher, P. T.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 509. (b) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.
(11) (a) Blaser, D.; Ko, S. Y.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 6230. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151. (d) Schmidt, U.; Respondek, M.; Lieberknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256. (e) Saito, S.; Takahashi, N.; Ishikawa, T.; Moriwake, T. *Tetahedron Lett.* **1991**, *32*, 667. (f) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866. (g) Nakatsuka, T.; Miwa, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 279. (h) Belokon', Yu. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Yu. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryapkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252. (i) Reno, D. S.; Lotz, B. T.; Miller, M. J. *Tetrahedron Lett.* **1990**, *31*, 827. (j) Gasparski, C. M.; Miller, M. J. *Tetrahedron* **1991**, *47*, 5367.
(12) *The Practice of Peptide Synthesis*; Bodanszky, M., Bodanszky, A., Eds.; Springer-Verlag: New York, 1984; p 259.
(13) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, *26*, 2525.
(14) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651.
(15) Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme IV

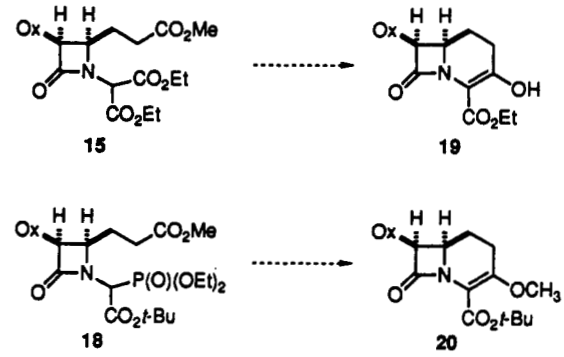


proton NMR, and they were found to be cis, with a coupling constant of 5.1 Hz for the C_3–C_4 protons. Extrapolating back to the aldol product indicated that the anti stereochemistry had been established in the condensation, which was the relative configuration we desired.

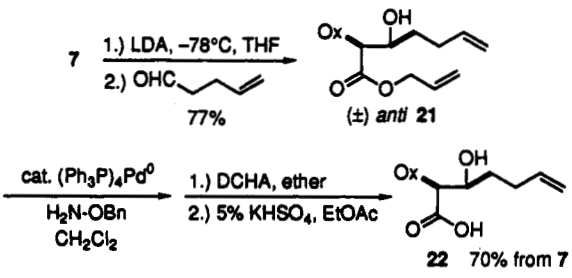
Since amino acid **10** had six of the eight carbons required for the fundamental carbacephem structure, our next step was incorporation of the other two carbon atoms, along with what would become the β-lactam nitrogen. The amino acid was thus coupled to either of two glycine derivatives, diethyl aminomalonate (**13**) or *tert*-butyl aminodiethylphosphonoacetate (**16**) (Scheme IV). These glycine derivatives were selected so that their appended functionality could be used for later completion of the carbacephem nucleus. Each coupling reaction was tried with various coupling reagents; those which gave the most satisfactory results are shown. Thus, DCC and *N*-hydroxysuccinimide produced dipeptide **14** in 33% yield after purification, while **17** was generated in 45% yield by an EEDQ-mediated coupling. Mitsunobu cyclizations were again carried out, using di-*tert*-butyl azodicarboxylate (DBAD), to prepare **15** in 61% yield and DIAD to prepare **18** in 80% yield. DBAD was used for the cyclization of malonate **14** since we have previously shown that cyclization of related amino malonates with less sterically demanding azodicarboxylates results in competitive formation of Michael addition products of the malonate to the azodicarboxylate.[16a] Cyclization of aminophosphonates is less sensitive to the nature of the azodicarboxylate.[16b] Townsend has also shown that modifications of the standard Mitsunobu conditions influence the effectiveness of the cyclization of serylphenylglycines and related peptides to β-lactams.[16c] Each β-lactam again showed the cis relationship of the C_3 and C_4 substituents, as expected. Attempted cyclizations of **15** → **19** and **18** → **20** (Scheme V) failed under a variety of conditions, apparently due to insufficient reactivity of the methyl ester moiety on the C_4 side chain.

Since the methyl ester of **15** and **18** was apparently not reactive enough to undergo the desired reactions, a more reactive carbonyl species was used instead. This was an aldehyde, masked as an olefin through the earlier steps of the synthetic sequence. The aldehyde employed was 4-pentenal, prepared by PCC oxidation of 4-pentenol in 30–50% yield, and this aldehyde was used for an aldol condensation (Scheme VI), carried out under the same

Scheme V



Scheme VI



conditions as in the earlier case. Deprotection of the allyl ester of **21** and purification by conversion to the DCHA salt and back to the free acid gave **22** in 70% overall yield for the aldol condensation, deprotection, and purification steps.

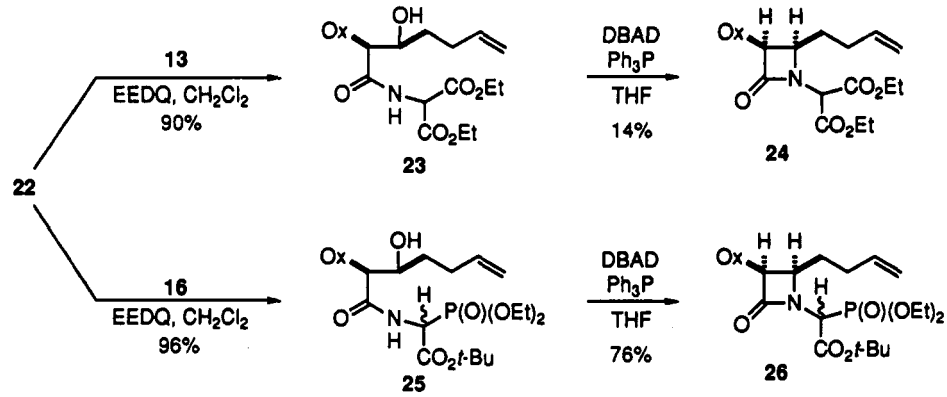
Amino acid **22** was coupled to glycine derivatives **13** and **16** using EEDQ in each case (Scheme VII). Dipeptides **23** and **25** were then isolated in 90% and 96% yields, respectively, and each was cyclized to a β-lactam via Mitsunobu reaction (DBAD, Ph_3P). Phosphonate-containing β-lactam **26** was collected in 76% yield, while the malonate-containing compound (**24**) was recovered in only 14%. This low yield was apparently the result of decomposition on silica gel during chromatography, as TLC during the reaction had indicated much more substantial conversion to product.

At this point, it was possible to attempt the second cyclization of both **24** and **26** be revealing the latent aldehyde in each that had been masked as an olefin. Precedent[17] exists for the spontaneous cyclization between an aldehyde and a malonate in a structure like **27**, which might be derived from **24** (Scheme VIII). The only

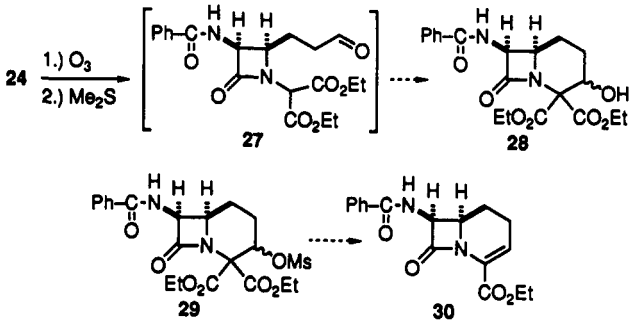
(16) (a) Miller, M. J.; Mattingly, P. G. *Tetrahedron* **1983**, *39*, 2563. (b) Huang, N. Z.; Kalish, V. J.; Miller, M. J. *Tetrahedron* **1990**, *46*, 8067. (c) Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 760 and refs therein.

(17) Mochida, K.; Hirata, T. *Chem. Pharm. Bull.* **1988**, *36*, 3642.

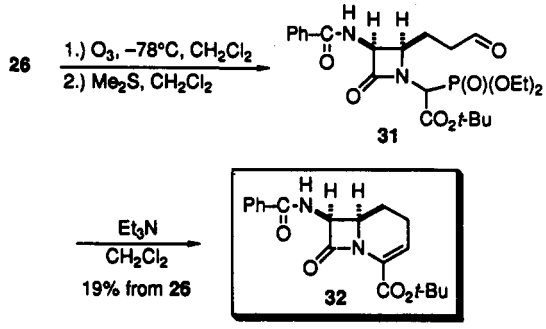
Scheme VII



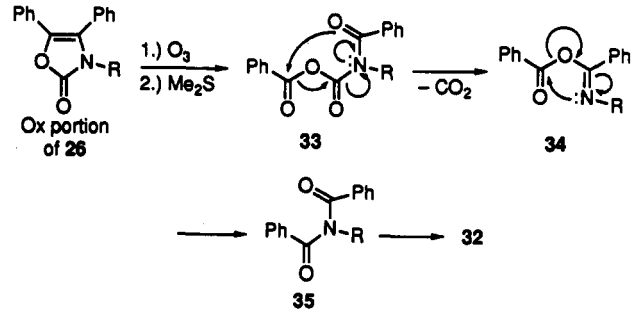
Scheme VIII



Scheme IX



Scheme X



structural difference between the aldehydic compound in the literature precedent and **27** proposed here was the presence of a benzamide group in our case, as opposed to a phthalimide in the literature example. As shown, the Ox group was expected to be cleaved to a benzamide by the ozonolysis. The proposed basis for this conversion will be discussed shortly.

Upon ozonolysis of **24**, the presence of an aldehydic compound, possibly **27**, was detected. However, the formation of expected carbacepham **28** could not be confirmed, and thus subsequent modifications to **29** and then carbacephem **30** could not be addressed. A low mass recovery in the ozonolysis suggested that most of the starting material may have decomposed, possibly due to the presence of other reactive intermediates arising from ozonolysis of the Ox group.

Cyclization of the other monocyclic β-lactam synthesized above (**26**) was carried out by first performing an ozonolysis and reductive workup to generate aldehyde **31** (Scheme IX). The proton NMR spectrum of the crude reaction product showed two aldehyde peaks (δ 9.658 and 9.677 ppm), which corresponded to the two diastereomers resulting from the racemic phosphonoacetate. Rather than isolating the aldehydes, the crude product mixture was treated with triethylamine to induce a Horner–Emmons cyclization. While the methyl ester of **18** previously had proven too unreactive to undergo such a cyclization, the aldehyde group of **31** reacted rapidly once the mild base was added. The aldehyde signals were absent from the NMR spectrum of the reaction mixture, and carbacephem **32** was successfully isolated and characterized. Thus, the one-pot transformation of β-lactam **26** included conversion of the olefin to an aldehyde, cleavage of the Ox group to a benzamide, and subsequent cyclization to carbacephem **32**. For this series of reactions an overall yield of 19% was realized.

500-MHz proton NMR analysis demonstrated that the Ox group had been cleaved to a benzamide as shown in carbacephem **32**. This was a fortuitous transformation, since removal of the Ox group is often a difficult reaction, usually performed by hydrogenation using elevated pressures and extended reaction times. Removal of the benzamide, in contrast, is more readily accomplished.[18] Simultaneous cleavage of the Ox group during aldehyde synthesis was, therefore, a synthetic advantage of this group.

The isolated benzamide probably arose as shown in Scheme X, which focuses on the oxazolinone portion of the compounds during the reaction **26** → **32**. The initial reduction product after ozonolysis of the Ox group in **26** would be imido anhydride **33**, which may then rearrange to ester imidate **34**. A subsequent Chapman rearrangement[19] to produce imide **35** is consistent with previous results obtained in our laboratory.[20,21] In those earlier

(18) Koppel, G. A.; McShane, L.; Jose, F.; Cooper, R. D. G. *J. Am. Chem. Soc.* **1978**, *100*, 3933.
(19) (a) Stevens, C. L.; Munk, M. E. *J. Am. Chem. Soc.* **1958**, *80*, 4065. (b) Stevens, C. L.; Munk, M. E. *J. Am. Chem. Soc.* **1958**, *80*, 4069. (c) Woodman, D. J.; Davidson, A. I. *J. Org. Chem.* **1970**, *35*, 83. (d) Curtin, D. Y.; Miller, L. L. *J. Am. Chem. Soc.* **1967**, *89*, 637.
(20) Farouz, F.; Miller, M. J. *Tetrahedron Lett.* **1991**, *32*, 3305.
(21) Farouz, F.; Miller, M. J. Manuscript in preparation.

studies, ozonolysis of the Ox group located at C_3 of a monocyclic β-lactam resulted in isolation of either an imide or an amide. An interesting observation was that when β-lactams lacking a C_4 substituent were ozonolyzed, the C_3 imide was isolated, while ozonolysis of C_4 substituted β-lactams gave the C_3 amide, as in **32**. If imide **35** was in fact an intermediate in the ozonolysis of **26**, then the imide functionality was extremely labile and was nearly quantitatively hydrolyzed to the benzamide, providing **32**. NMR spectra showed only a single carbacephem to be present, not a mixture of two or more. While the product obtained was unsubstituted at the C_3 position (cephem numbering), methods of functionalizing carbacephems at this position are well-known,[2a,22] which suggests that a wide variety of C_3 derivatives can be accessed in very few steps.

Conclusion

The series of reactions described here has successfully produced the carbacephem framework as a single diastereomer in relatively few steps. Although the yield in the final ring closing sequence was not high, several chemical transformations were involved. The key step in the synthesis was an aldol condensation that provided, in a single step, most of the carbon atoms found in the target compound, as well as functional groups and the stereochemistry required for biological activity in this promising class of antibiotics. Versatility of the method lies in the fact that the aldehyde used in the aldol reaction may be structurally varied to suit the particular needs of the synthetic chemist. Additionally, a convenient and high yielding method of preparing anti β-hydroxy-α-amino acids has been demonstrated.

Experimental Section

General Methods. Reagents and solvents used in synthetic work were obtained commercially, unless otherwise noted. Chemicals were reagent grade and were used without further purification unless otherwise specified; solvents were distilled and, when necessary, dried by standard methods[23] before use. Concentration of *n*-BuLi was determined by titration with 1.000 M *sec*-butyl alcohol in dry toluene using 1,10-phenanthroline as indicator.[24]

Instruments and general chromatographic methods used have been described previously.[25] Additionally, ^{31}P NMR spectra were obtained on a Nicolet NB-300 spectrometer in $CDCl_3$ with concentrated phosphoric acid (H_3PO_4) as external reference (δ = 0.000 ppm).

Methyl 4-Pentenoate (3). 4-Pentenoic acid (16.2 mL, 159 mmol) was placed in a nitrogen-purged flask and cooled to 0 °C. Oxalyl chloride (15.2 mL, 175 mmol, 1.1 equiv) was added neat via syringe over 15 min. The reaction was stirred at 0 °C for 3 h and then at rt for 17 h. The acid chloride was present as a yellow slurry. The flask was again cooled to 0 °C, and dry MeOH (26 mL, 636 mmol, 4 equiv) was added slowly from a syringe. The reaction was stirred for 1.5 h at 0 °C and then 4 h at rt. The mixture was distilled under vacuum to give a mixture of methyl pentenoate (bp = 20–22 °C (1 mmHg)) and MeOH. Addition of water formed two layers; the top layer was removed, dried ($MgSO_4$), and filtered to give pure methyl 4-pentenoate (82%, 14.7 g, 130 mmol). R_f = 0.72 (30% ethyl acetate (EtOAc) in hexanes).

^{1}H NMR (300 MHz): δ 2.39 (4 H, m), 3.67 (3 H, s), 5.02 (2 H, m), 5.81 (1 H, m). ^{13}C NMR: δ 28.63, 33.11, 51.21, 115.20, 136.44, 173.17. HRMS: *m/e* 114.06808 calcd for $C_6H_{10}O_2$, 114.0684 found. IR (thin film): 2960, 1746, 1642, 1438 cm^{-1}.

Succinic Semialdehyde Methyl Ester (4). Methyl 4-pentenoate (**3**) (14.7 g, 130 mmol) was dissolved in 25 mL of CH_2Cl_2 and cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. The excess ozone was expelled by bubbling N_2 through the reaction mixture, and then Me_2S (28.4 mL, 387 mmol, 3 equiv) was added. The mixture was allowed to reach rt as it stirred overnight. The crude product was eluted through a silica column (25 × 300 mm) three times with CH_2Cl_2 to remove DMSO. After distillation, succinic semialdehyde methyl ester **4** (bp = 55–60 °C (3 mmHg)) was isolated in 51% yield (7.7 g, 66.3 mmol). R_f = 0.19 (20% EtOAc in hexanes).

^{1}H NMR: δ 2.64 (2 H, t, J = 6.3 Hz), 2.81 (2 H, dt, J = 6.3 and 0.6 Hz), 3.70 (3 H, s), 9.8 (1 H, s). ^{13}C NMR: δ 27.43, 29.03, 51.31, 99.32 (imp), 173.96, 173.19, 199.80. HRMS: *m/e* 115.0392 calcd for $C_5H_7O_3$ (M − H), 115.0395 found. IR (thin film): 2960, 2845, 2740, 1730, 1475 cm^{-1}.

3-(Carboxymethyl)-4,5-diphenyl-1-oxazolin-2-one (6).[5] To a 25 wt % solution of tetramethylammonium hydroxide (27 mL, 64 mmol) was added glycine (4.8 g, 64 mmol). The glycine dissolved, and the solution was condensed by water aspirator vacuum on a rotary evaporator. The colorless oil was taken up in 65 mL of DMF and was chilled in an ice bath. Carbonate **5**[5] (15.3 g, 64 mmol) was dissolved in 50 mL of DMF, and the solution was added to the chilled glycine salt solution. The flask was removed from the ice bath and was stirred for 30 min. HCl (2 M; 65 mL) was added, followed by 200 mL of EtOAc. The layers were separated, the aqueous DMF layer was extracted with 100 mL of EtOAc, and the EtOAc layers were combined. The EtOAc solution was washed with water (3 × 75 mL), dried ($MgSO_4$), filtered, and condensed to give the intermediate hydroxyoxazolidinone as a white solid. To the solid was added trifluoroacetic acid (TFA; 65 mL), and the solution was stirred overnight. The solvent was removed under high vacuum to give an amber oil. The oil was dissolved in CH_2Cl_2 (150 mL), washed with water (3 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to give an off-white solid. The crude product was recrystallized from hot $CHCl_3$ to give **6** as large, colorless crystals (mp = 175.5–176.0 °C) in 65% yield (12.2 g, 41.7 mmol).

^{1}H NMR (DMSO-d_6): δ 4.11 (2 H, s), 7.2–7.6 (10 H, m), 13.22 (1 H, s). ^{13}C NMR ($CDCl_3$): δ 42.83, 122.96, 124.51, 126.26, 127.37, 128.01, 128.49, 129.79, 130.42, 130.53, 135.26, 154.85, 171.61. HRMS: *m/e* 295.084 46 calcd for $C_{17}H_{13}O_4N$, 295.0852 found. IR ($CHCl_3$): 3010 (w), 1770 (br), 1705, 1445, 1215, 900 cm^{-1}.

3-(((Allyloxy)carbonyl)methyl)-4,5-diphenyl-1-oxazolin-2-one (7).[6] Ox-glycine **6** (504 mg, 1.7 mmol) was dissolved in 10 mL of DMF. Solid, anhydrous K_2CO_3 (263 mg, 1.1 equiv) was added, followed by allyl bromide (225 μL, 2.5 mmol, 1.5 equiv). Some solid K_2CO_3 remained, but by 1 h, TLC showed the reaction to be complete. EtOAc (50 mL) was added to the reaction mixture, and the solution was washed with saturated NaCl (2 × 40 mL), water (1 × 40 mL), and saturated $NaHCO_3$ (2 × 40 mL). The solution was dried ($MgSO_4$), filtered, and condensed to an oil. The oil was crystallized from either $CHCl_3$ or CH_2Cl_2. The yield of crystalline (mp = 86–88 °C) **7** was 94% (539 mg, 1.61 mmol). R_f = 0.65 (40% EtOAc in hexanes).

^{1}H NMR: δ 4.22 (2 H, s), 4.59 (2 H, d, J = 4.5 Hz), 5.2–5.3 (2 H, m), 5.75–5.90 (1 H, m), 7.1–7.5 (10 H, m). ^{13}C NMR: δ 42.94, 66.08, 118.84, 122.81, 124.28, 126.44, 127.43, 127.69, 128.31, 129.45, 130.20, 130.29, 130.95, 134.69, 154.28, 166.99. CIMS (isobutane): *m/e* 336 (M + H). IR ($CHCl_3$): 1765, 1750, 1600, 1410, 1200 cm^{-1}.

(±)-*anti*-2-(2-Oxo-4,5-diphenyl-1-oxazolinyl)-3-hydroxyadipic Acid 1-Allyl 6-Methyl Diester (8). Dry THF (10 mL) was placed in a flask and cooled in an ice bath. Diisopropylamine (273 μL, 1.95 mmol, 1.4 equiv) was added, followed by *n*-BuLi (1.66 M in hexanes; 880 μL, 1.46 mmol, 1.05 equiv). The flask was cooled to −78 °C in a dry ice/acetone bath and stirred for 20 min. The allyl ester of Ox-glycine (**7**; 467 mg, 1.39 mmol, 1.0 equiv) was dissolved in 5 mL of THF and added to the chilled solution over ~1 min. After the solution was stirred for 1 additional h, succinic semialdehyde methyl ester (**4**; 337 mg, 2.0 eq) was added dropwise, and the reaction was stirred for 1 h at −78 °C. While still at this temperature, 30 mL of potassium phosphate (KP_i) buffer (100 mM, pH = 7.5) was added, providing

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2 equiv of phosphate. After being warmed to rt, the mixture was extracted with EtOAc (5 × 30 mL). The organic solution was dried ($MgSO_4$), filtered, and condensed to a yellow oil. After column chromatography (40% EtOAc in hexanes), a 92% yield (580 mg, 1.28 mmol) was obtained as an oil. R_f = 0.43 (40% EtOAc in hexanes).

^{1}H NMR: δ 1.88 (2 H, m), 2.45 (2 H, m), 3.65 (3 H, s), 3.68 (<1 H, imp), 3.987 (1 H, d, J = 5.1 Hz, αH), 4.45 (~2 H, m, βH plus <1 H imp), 4.69 (2 H, d, J = 5.7 Hz), 5.2–5.4 (2 H, m), 5.9–6.0 (1 H, m), 7.2–7.6 (10 H, m). ^{13}C NMR: δ 28.53, 29.76, 51.22, 60.47, 66.29, 68.77, 118.74, 123.05, 124.07, 125.82, 126.98, 127.75, 128.21, 129.60, 130.47, 130.55, 130.82, 135.18, 154.04, 167.73, 173.32. EIMS: m/e 452 (M + H). IR (thin film): 3440 (br), 1770, 1735, 1650, 1600, 1500, 1260 cm^{-1}.

(±)-*anti*-2-(2-Oxo-4,5-diphenyl-1-oxazolinyl)-3-hydroxyadipic Acid 6-Methyl Ester (10). Allyl ester 8 (1.08 g, 2.39 mmol) was dissolved in 10 mL of dry CH_2Cl_2, and to this was added a solution of O-benzylhydroxylamine (0.30 g, 1.0 equiv) in 10 mL of CH_2Cl_2. Tetrakistriphenylphosphine palladium(0) (0.276 g, 0.10 equiv) was added as the solid, and the reaction was stirred under N_2 while shielded from light. After 4 h the solvent was stripped and the oil was dissolved in 45 mL of EtOAc and washed with HCl (1 M; 5 × 25 mL), water (25 mL), and brine (25 mL). The organic solution was dried ($MgSO_4$) and filtered, and the solvent was stripped in vacuo. The crude product (1.163 g) was dissolved in 7 mL of ether. Dicyclohexylamine (DCHA; 460 μL, 1.0 equiv based on theoretical yield) was added, and the tan precipitate (**9**) that formed was filtered and washed with ether. The yield for the deprotection and salt formation was 81% (1.15 g, 1.94 mmol).

Salt **9** was converted, in some cases, to free acid **10** as follows: The DCHA salt (8.12 g, 13.7 mmol) was added to a vigorously stirred biphasic system of 5% aqueous $KHSO_4$ (150 mL) and EtOAc (250 mL).[12] After the salt had completely dissolved (less than 3 min), the layers were separated, the aqueous solution was extracted with EtOAc, and the combined organic solutions were washed with water (5×), dried ($MgSO_4$), and filtered. The solvent was stripped to yield a yellow oil. Attempted crystallization of the free acid was unsuccessful. Yield for the conversion to the free acid was 96.4% (5.43 g, 13.2 mmol).

10. ^{1}H NMR: δ 1.86 (1 H, m), 2.48 (3 H, m), 3.66 (3 H, s), 3.95 (1 H, d, J = 5.6 Hz), 4.46 (1 H, m), 7.2–7.6 (10 H, m). CIMS (isobutane): m/e 412 (M + H). IR (thin film): 3450 (br), 1745, 1500, 1440, 1370 cm^{-1}.

9. Mp = 195–196 °C dec. Anal. Calcd for $C_{34}H_{44}N_2O_7$: C, 68.9; H, 7.48; N, 4.73. Found: C, 69.35; H, 7.46; N, 4.74.

(±)-*anti*-2-(2-Oxo-4,5-diphenyl-1-oxazolinyl)-3-hydroxyadipohydroxamate 1-*O*-Benzyl 6-Methyl Ester (11). DCHA salt **9** (0.500 g, 0.844 mmol) was dissolved in warm (~40 °C) DMF, and the solution was added to 20 mL of a 1:1 mixture of water/DMF. Dicyclohexylamine (162 μL, 1.0 equiv) was added, followed by O-benzylhydroxylamine hydrochloride (139 mg, 1.0 equiv). The pH of the mixture was determined to be 4.7. 1-(3-(Dimethylamino)propyl)-3-ethylcarbodiimide[13] (WSC; 164 mg, 1.0 equiv) was dissolved in water (5 mL) and added to the other reactants. The pH was monitored and controlled with a pH stat, but the pH stabilized at ~4.2 and remained there without any further adjustment. After 53 min, the mixture was extracted with EtOAc (3 × 50 mL) and the organic solution was washed with citric acid (1 M; 2×), 5% $NaHCO_3$ (2×), and brine (1×). The organic solution was dried ($MgSO_4$), filtered, and condensed to an oil. The oil was dissolved in EtOAc and passed through a silica column (4 × 30 mm) to remove almost all of the DMF remaining after the acid wash. The yield of the hydroxamate was 69% (0.30 g, 0.58 mmol). R_f = 0.19 (40% EtOAc in hexanes).

^{1}H NMR: δ 1.6 (1 H, m), 1.8 (1 H, m), 2.4 (2 H, m), 3.6 (3 H, s), 3.92 (1 H, d, J = 8.7 Hz), 4.02 (s, imp), 4.4 (1 H, m), 4.9 (2 H, s), 7.1–7.6 (~15 H, m). CIMS (isobutane): m/e 517 (M + H). IR ($CHCl_3$): 3280 (br), 3010, 1750, 1700, 1600 (w), 1500, 1440, 1360 cm^{-1}.

(±)-*N*-(Benzyloxy)-3-(2-oxo-4,5-diphenyl-1-oxazolinyl)-4-(2-carbomethoxyethyl)azetidin-2-one (12). Hydroxamate **11** (349 mg, 0.676 mmol) was dissolved in 5 mL of dry THF and added to a solution of triphenylphosphine (186 mg, 1.05 equiv) in 5 mL of THF. This solution was cooled to −20 °C, and a solution of diisopropylazodicarboxylate (DIAD; 140 μL, 1.05 equiv) in 2 mL of THF was added slowly via cannula.[15] The solution was stirred under argon, protected from light. After 1 h, the reaction was brought to room temperature. After a total of 48 h, the solvent was evaporated. After column chromatography (40% EtOAc in hexanes), 194 mg of the β-lactam was collected (57%, 0.385 mmol). R_f = 0.42 (40% EtOAc in hexanes).

^{1}H NMR: δ 1.9 (2 H, m), 2.28 (2 H, t, J = 7.2 Hz), 3.66 (3 H, s), 3.73 (1 H, d of t, J = 7.8, 5.3 Hz), 4.44 (1 H, d, J = 3.9 Hz), 5.02 (2 H, d of d, J = 10.9, 11.0 Hz), 7.22–7.55 (10 H, m). ^{13}C NMR: δ 23.85, 30.08, 51.76, 56.89, 63.24, 78.78, 122.69, 124.59, 125.93, 127.12, 128.20, 128.51, 128.65, 129.16, 129.72, 129.82, 130.58, 130.72, 134.59, 135.57, 154.28, 159.26, 172.53. CIMS (isobutane): m/e 499 (M + H). IR ($CHCl_3$): 3020, 1785, 1762, 1220 cm^{-1}.

(±)-*anti*-*N*-(Bis(ethoxycarbonyl)methyl)-2-(2-oxo-4,5-diphenyl-1-oxazolinyl)-3-hydroxyadipamide 6-Methyl Ester (14). Carboxylic acid **10** (0.497 g, 1.21 mmol) was dissolved in 10 mL of dry CH_3CN. To this solution was added triethylamine (170 μL, 2.0 equiv), N-hydroxysuccinimide (139 mg, 1.0 equiv), and diethyl aminomalonate hydrochloride (256 mg, 1.0 equiv). After the mixture was cooled to −14 °C, DCC (250 mg, 1.0 equiv) was added. After 24 h, the precipitated dicyclohexylurea (DCU) was filtered off and the remaining solution was condensed to a yellow oil. The oil was redissolved in EtOAc (20 mL) and washed with saturated $NaHCO_3$ (3 mL), citric acid (1 M; 5 mL), saturated $NaHCO_3$ (5 mL), and water (5 mL). The organic solution was dried ($MgSO_4$), filtered, and condensed to a yellow oil. The crude product was purified by radial chromatography (20% isopropyl alcohol (IPA) in hexanes) to yield 33% (226 mg, 0.40 mmol) of the dipeptide as a yellow oil. R_f = 0.22 (40% EtOAc in hexanes), 0.52 (20% IPA in hexanes).

^{1}H NMR: δ 1.30 (8 H, dt, J = 7.2, 3 Hz), 1.7 (1 H, m), 1.85 (1 H, m), 2.45 (2 H, m), 2.66 (3 H, s), 3.95 (1 H, d, J = 8.1 Hz), 4.28 (5 H, m) 4.38 (1 H, d, J = 3.6 Hz), 4.58 (1 H, m), 5.15 (1 H, d, J = 6.6 Hz), 7.2–7.6 (13 H, m), 8.29 (1 H, d, J = 6.6 Hz). ^{13}C NMR: δ 24.82, 28.72, 29.83, 33.72, 51.75, 56.76, 60.63, 62.59, 62.62, 68.70, 123.55, 124.35, 126.08, 127.26, 127.83, 128.32, 129.69, 130.46, 130.92, 135.40, 154.31, 165.86, 167.72, 174.28. MS (positive FAB, 50/50 glycerol/NBA): m/e 569 (M + H). IR (thin film): 3340, 2980, 1750, 1675, 1600, 1520 cm^{-1}.

(±)-*anti*-*N*-((*tert*-Butoxycarbonyl)(diethylphosphono)-methyl)-2-(2-oxo-4,5-diphenyl-1-oxazolinyl)-3-hydroxyadipamide 6-Methyl Ester (17). Carboxylic acid **10** (976 mg, 2.37 mmol) was dissolved in 15 mL of dry CH_2Cl_2, and aminodiethylphosphonoacetate *tert*-butyl ester (**16**)[26] (665 mg, 1.05 equiv) was added, followed by EEDQ (645 mg, 1.1 equiv). The reaction was monitored by TLC. At 19 h, additional EEDQ (300 mg, 0.5 equiv) was added. After a total of 21 h, the solvent was stripped, the remaining oil was redissolved in EtOAc, and the organic solution was washed with citric acid (1 M; 3 × 50 mL), water (50 mL), and 5% $NaHCO_3$ (2 × 50 mL). After the solution was dried ($MgSO_4$), filtered, and condensed to a brown oil, the crude product was purified by radial chromatography (eluted with 20% IPA/hexanes) to give **17** as an oil in 26% yield (0.78 mmol, 514 mg). R_f = 0.53 (neat EtOAc), 0.52 (20% IPA in hexanes).

^{1}H NMR: δ 1.327 (12 H, m), 1.481 (9 H, s), 1.502 (9 H, s), 1.7 (2 H, m), 1.9 (2 H, m), 2.46 (4 H, m), 3.644 (3 H, s), 3.650 (3 H, s), 3.86 (1 H, d, J = 3.3 Hz), 3.90 (1 H, d, J = 2.7 Hz), 4.18 (8 H, m), 4.63 (2 H, m), 4.84 (1 H, d, J = 4.2 Hz), 4.89 (1 H, d, J = 4.2 Hz), 5.02 (1 H, dd, J_{HH} = 8.6 Hz, J_{HP} = 21.3 Hz), 5.09 (1 H, d, J = 8.7 Hz), 7.2–7.6 (20 H, m). ^{13}C NMR: δ 14.3, 16.04, 16.12, 16.18, 27.6, 28.64, 28.89, 29.6, 50.73, 50.89, 51.39, 51.47, 51.52, 51.95, 52.65, 52.79, 53.1, 60.5, 61.42, 61.56, 63.13, 63.22, 63.29, 63.37, 63.46, 63.52, 63.64, 63.73, 67.91, 68.20, 83.2, 83.39, 83.42, 123.6, 124.21, 124.25, 125.96, 126.15, 127.14, 127.29, 127.65, 127.78, 128.21, 128.23, 129.6, 130.31, 130.34, 130.87, 135.12, 135.31, 154.04, 154.29, 164.54, 165.00, 165.55, 167.62, 167.70, 173.87, 173.98. MS (positive FAB, 50/50 glycerol/NBA): m/e 661 (M + H). IR (thin film): 3020, 1740, 1685, 1500, 1215 cm^{-1}.

(±)-*N*-(Bis(ethoxycarbonyl)methyl)-3-(2-oxo-4,5-diphenyl-1-oxazolinyl)-4-(2-carbomethoxyethyl)azetidin-2-one (15). Dipeptide **14** (226 mg, 0.397 mmol) was dissolved in 15 mL of dry

(26) Compound **16** was the generous gift of Eli Lilly and Co.

THF and cooled to −15 °C. Triphenylphosphine (135 mg in 5 mL of THF, 1.3 equiv) was added, followed by di-*tert*-butyl azodicarboxylate (DBAD; 120 mg in 5 mL of THF, 1.3 equiv). The reaction was stirred under nitrogen and shielded from light. The solution was warmed to 10 °C overnight, by which time TLC showed a new, blue (under UV) spot at higher R_f than starting material, but this spot did not increase in intensity even after 20 h at 40 °C. At 42 h the solution was cooled to −10 °C, and an additional 1.0 equiv each of triphenylphosphine (104 mg in 5 mL of THF) and DBAD (91 mg in 5 mL of THF) were added. After 2 h the solution was warmed again to 40 °C. After a total of 69 h, the solvent was stripped, ether (~10 mL) was added to precipitate triphenylphosphine oxide, and the remaining material was subjected to radial chromatography (20% IPA/hexanes). Yield of product (still with traces of starting material) was 61% (133 mg, 0.24 mmol). Attempted crystallization of the oil was unsuccessful. R_f = 0.48 (20% IPA in hexanes).

^{1}H NMR: δ 1.275 (9 H, t, J = 7.2 Hz), 2.24 (m), 2.35 (m), 2.45 (m) [δ 2.24–2.45 integrate to 4 H], 3.764 (3 H, s), 4.270 (q, J = 11.7 Hz), 4.30 (m) [preceding two signals integrate to 5 H], 4.77 (1 H, d, J = 4.8 Hz), 5.304 (1 H, s), 7.1–7.8 (~60 H, m). ^{13}C NMR: δ 3.78, 13.73, 13.77, 23.81, 30.40, 31.41, 51.60, 51.66, 56.5, 57.04, 59.84, 60.24, 62.58, 62.66, 124.45, 128.23, 128.39, 129.73, 129.87, 130.47, 130.55, 131.75, 131.78, 131.83, 131.96, 132.95, 141.47, 153.36, 162.03, 163.55, 164.64, 164.80, 165.47, 165.61, 172.11, 172.58. HRMS: m/e 550.195 133 calcd for $C_{29}H_{30}N_2O_9$, 550.1945 found. IR (thin film): 1770, 1740, 1440, 1020 cm^{-1}.

(±)-*N*-((*tert*-Butoxycarbonyl)(diethylphosphono)methyl)-3-(2-oxo-4,5-diphenyl-1-oxazolinyl)-4-(2-carbomethoxyethyl)azetidin-2-one (18). Dipeptide 17 (203 mg, 0.307 mmol) was dissolved in 7 mL of dry THF and cooled to −15 °C. Triphenylphosphine (89 mg in 5 mL of THF, 1.1 equiv) was added, followed by diisopropyl azodicarboxylate (DIAD; 67 μL in 1 mL of THF, 1.1 equiv). The reaction was stirred under nitrogen and protected from light. After 1 h, the flask was warmed to room temperature. After 24 h, an additional 0.5 equiv each of triphenylphosphine (40 mg in 2 mL of THF) and DIAD (30 μL neat) were added. After a total of 44 h, the solvent was stripped, triphenylphosphine oxide was precipitated with ether, and the material was purified by radial chromatography (20% IPA/hexanes). The yield of the β-lactam was 80.1% (158 mg, 0.246 mmol). Attempted crystallization of the oil was unsuccessful. R_f = 0.36 (20% IPA in hexanes).

^{1}H NMR: δ 1.31 (dt, J = 6.9, 2.1 Hz), 1.394 (t, J = 7.2 Hz), 1.412 (t, J = 6.9 Hz), 1.475 (s), 1.524 (s) [All of the preceding signals collectively integrate to 30 H, for both diastereomers], 2.24 (2 H, m), 2.53 (4 H, m), 3.634 (1 H, d, J = 6.3 Hz), 3.644 (3 H, s), 3.675 (3 H, s), 4.1–4.35, (8 H, 2m), 4.43 (1 H, m), 4.73 (1 H, m), 5.01 (1 H, d, J_{HP} = 24.3 Hz), 5.043 (1 H, d, J_{HP} = 24.0 Hz), 7.2–7.6 (20 H, m). ^{13}C-NMR: δ 16.20, 16.24, 16.28, 16.32, 16.35, 16.43, 23.73, 24.50, 27.84, 27.91, 30.55, 30.64, 51.66, 52.78, 53.72, 54.71, 60.21, 60.42, 60.65, 61.00, 63.43, 63.52, 63.66, 63.74, 63.84, 84.04, 84.32, 122.86, 124.62, 126.05, 127.32, 128.12, 128.50, 129.82, 129.89, 130.53, 130.57, 130.75, 130.80, 135.56, 135.62, 153.29, 153.55, 163.86, 163.92, 164.08, 164.13, 164.20, 164.28, 172.97, 173.03. ^{31}P-NMR (121.5 MHz, $CDCl_3$): δ 14.7 (m). ^{1}H-decoupled ^{31}P spectrum: δ 14.646 (s), 14.741 (s). MS (positive FAB, 50/50 glycerol/NBA): m/e 643 (M + H). IR (thin film): 1760, 1735, 1020, 910 cm^{-1}.

4-Pentenal. Activated 4-Å molecular sieves (35 g) were ground and placed into a 500-mL round-bottom flask along with oven-dried sodium acetate (53 g, 0.696 mol, 6.0 equiv). Dry CH_2Cl_2 (300 mL) and pyridinium chlorochromate (PCC; 50.0 g, 1.39 mol, 2.0 equiv) were added, and the flask was cooled in an ice bath. Neat 4-pentenol (10.0 g, 0.116 mol) was added slowly. The reaction mixture was swirled on a platform shaker. After 2 h, the ice bath was removed and the reaction continued for 2 h more at rt. Ether (200 mL) was added, and the mixture was filtered through Celite and Florisil twice to remove nearly all color and chromium salts. The volume was reduced by two-thirds by distilling the solvents off using a 30-cm Vigreux column. The remaining solution was distilled with a 15-cm vacuum-jacketed Vigreux column. The product was collected at 90–120 °C to give a 50% yield (4.9 g, 0.058 mol) of 4-pentenal.

^{1}H NMR: δ 2.41 (2 H, m), 2.56 (2 H, m), 5.04 (2 H, m), 5.82 (1 H, m), 9.78 (1 H, t, J = 1.5 Hz).

(±)-*anti*-3-Hydroxy-2-(2-oxo-4,5-diphenyl-1-oxazolinyl)-7-heptenoic Acid Allyl Ester (21). Dry THF (25 mL) was cooled in an ice bath, and diisopropylamine (2.3 mL, 1.4 eq) was added. After the solution was cooled to −78 °C, *n*-BuLi (8.2 mL of a 1.6 M solution in hexanes, 1.1 equiv) was added. After 30 min, allyl Ox-glycine 7 (4.0 g, 0.0119 mol, 1.0 equiv) was added as a solution in 25 mL of THF. After the enolate solution had stirred for 1 h, 4-pentenal (2.086 g, 2.1 equiv) was added as a solution in 2 mL of THF. The reaction was stirred for 2 h, and then 50 mL of 1 M potassium phosphate (KP_i) buffer (pH 7.0) was added and the mixture was brought to room temperature. The mixture was extracted with EtOAc (2 × 50 mL), and the organic solution was dried ($MgSO_4$), filtered, and condensed to an orange oil. The oil was semipurified by radial chromatography (40% EtOAc in hexanes) to give a 77% yield (3.18 g, 7.57 mmol) of **21**. Alternatively, the crude aldol product could be used directly for allyl ester deprotection. R_f = 0.73 (40% EtOAc in hexanes).

^{1}H NMR: δ 1.6 (2 H, m), 2.1 (1 H, m), 2.2 (1 H, m), 4.00 (1 H, d, J = 4.8 Hz), 4.46 (1 H, m), 4.74 (2 H, m), 5.0 (2 H, m), 5.3 (2 H, m), 5.8 (1 H, m), 5.9 (1 H, m), 7.3 (11 H, m), 7.9 (0.5 H, m). CIMS (isobutane): m/e 420 (M + H). IR ($CHCl_3$): 3400, 2950, 1740 (br), 1690, 1641, 1601 cm^{-1}.

(±)-*anti*-3-Hydroxy-2-(2-oxo-4,5-diphenyl-1-oxazolinyl)-7-heptenoic Acid (22). Crude aldol product **21** (5.443 g, ~0.0119 mol with trace EtOAc and minor impurities, <5%) was dissolved in 25 mL of dry CH_2Cl_2. *O*-Benzylhydroxylamine (1.54 g, 1.05 equiv) was dissolved in 5 mL of CH_2Cl_2 and added to the first solution. Tetrakistriphenylphosphine palladium(0) (1.375 g, 0.10 equiv) was added and the reaction was stirred under argon, protected from light. After 18 h, the solvent was removed, the oil was redissolved in EtOAc (50 mL), and the solution was washed with HCl (1 M; 4 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL). After drying ($MgSO_4$), filtering, and condensing, an orange oil was obtained. This oil was dissolved in 20 mL of ether and 5 mL of EtOAc, and an ether solution of dicyclohexylamine (DCHA) was added to form the DCHA salt of the carboxylic acid. After the solution was cooled (ice bath) and the volume reduced, the precipitated salt was collected by centrifugation as a tan powder and was washed with ether. The salt was converted back to the free acid by stirring with a mixture of 5% $KHSO_4$ and EtOAc (~50 mL of each). The organic solution was dried ($MgSO_4$), filtered, and condensed. A pale yellow foam was recovered in 70.4% yield (3.181 g, 8.384 mmol) overall from allyl Ox-glycine 7.

^{1}H NMR: δ 1.6 (2 H, m), 2.1 (2 H, m), 3.97 (1 H, d, J = 5.4 Hz), 4.4 (1 H, m), 4.9 (2 H, m), 5.7 (1 H, m), 7.3 (11 H, m). ^{13}C NMR: δ 29.50, 31.31, 32.54, 60.00, 69.63, 115.36, 123.45, 124.43, 124.76, 125.92, 127.13, 128.10, 128.49, 129.24, 129.96, 130.81, 135.74, 137.44, 154.77, 171.23. HRMS: m/e 379.141 974 calcd for $C_{22}H_{21}NO_5$, 379.1421 found. IR (CCl_4): 3070, 1750 (br), 1490, 1375 cm^{-1}.

(±)-*anti*-*N*-(Bis(ethoxycarbonyl)methyl)-2-(2-oxo-4,5-diphenyl-1-oxazolinyl)-3-hydroxy-7-heptenamide (23). To a solution of carboxylic acid **22** (835 mg, 2.20 mmol) in 19.5 mL of CH_2Cl_2 was added diethyl aminomalonate hydrochloride (**13**) (490 mg, 1.05 equiv; Aldrich), followed by EEDQ (816 mg, 1.5 equiv). After 15 h, the solvent was stripped and the residue was dissolved in 50 mL of EtOAc. The solution was washed with citric acid (1 M; 3 × 50 mL), water (50 mL), and 5% $NaHCO_3$ (2 × 50 mL). The organic solution was dried with $MgSO_4$, filtered, and condensed to an oil. The crude product was purified by radial chromatography (2% IPA in hexanes) to give 90.4% (1.067 g, 1.99 mmol) of dipeptide **23** (still with a minor impurity). R_f = 0.74 (10% IPA in hexanes).

^{1}H NMR: δ 1.27 (t, J = 7.2 Hz, imp), 1.28 (t, J = 7.2 Hz) [two signals integrate to 11 H], 1.5 (1 H, m), 1.6 (1 H, m), 2.1 (2 H, m), 4.03 (1 H, d, J = 8.7 Hz), 4.11 (2 H, q, J = 7.1 Hz, imp), 4.25 (4 H, m), 4.54 (1 H, m), 5.0 (2 H, m), 5.16 (1 H, d, J = 6.6 Hz), 5.7 (1 H, m), 5.92 (0.8 H, d, J = 7.8 Hz), 7.4 (10 H, m), 8.46 (1 H, d, J = 6.3 Hz). ^{13}C NMR: δ 13.60, 14.08, 28.63, 32.94, 56.55, 57.38, 60.33, 61.25, 62.15, 62.26, 62.31, 68.40, 114.90, 123.48, 124.05, 125.99, 127.10, 127.55, 128.08, 129.39, 130.20, 130.72, 134.95, 137.33, 154.09, 155.37, 165.43, 165.66, 166.10, 167.78. HRMS: m/e 536.215 868 calcd for $C_{29}H_{32}N_2O_8$, 536.2151 found. IR (CCl_4): 3360, 2995, 1745, 1685, 1515 cm^{-1}.

(±)-*N*-(Bis(ethoxycarbonyl)methyl)-3-(4,5-diphenyl-1-oxazolinyl)-4-(4-butenyl)azetidin-2-one (24). Dipeptide **23** (960 mg, 1.79 mmol) was dissolved in 36 mL of dry THF and cooled to −20 °C. Triphenylphosphine (939 mg, 2.0 equiv) was added as a solution in 10 mL of THF, followed by di-*tert*-butyl azodicarboxylate (DBAD; 824 mg, 2.0 equiv), also as a solution in 10 mL of THF. The reaction mixture was allowed to reach room temperature overnight. After 17 h the solvent was stripped and the amber oil was redissolved in 50 mL of ether. A crystal of triphenylphosphine oxide (TPPO) was added to induce crystallization of the TPPO byproduct of the reaction. After the solid material was filtered off radial chromatography (2% IPA in hexanes) gave the product, still with an aromatic contaminant. The yield was 14% (125 mg, 0.241 mmol) with this impurity. From TLC monitoring of the reaction, actual chemical yield seemed much higher, and decomposition during chromatography apparently occurred. Attempted recrystallization of the product was unsuccessful. R_f = 0.78 (10% IPA in hexanes), R_f = 0.19 (40% EtOAc in hexanes).

^{1}H NMR: δ 1.28 and 1.35 (8 H [w/imp], 2t, J = 7.2 and 7.2 Hz), 1.47 (4 H, imp, m), 2.07 (4 H, m), 4.24 and 4.28 (5 H, 2q [plus overlapping signal], J = 7.05 and 7.05 Hz), 4.78 (1 H, br), 5.0 (2 H, m), 5.27 (1 H, s), 5.75 (1 H, m), 7.4 (16 H imp, m), 7.9 (1 H, m imp). ^{13}C NMR: δ 13.93, 13.95, 27.68, 27.93, 28.00, 28.20, 30.20, 57.13, 60.18, 60.33, 62.63, 62.79, 115.83, 120.68, 120.75, 122.77, 124.64, 126.12, 127.27, 128.18, 128.49, 128.54, 128.66, 129.62, 129.88, 130.65, 130.70, 131.73, 131.87, 132.44, 135.69, 136.80, 153.61, 163.84, 165.03, 165.17. HRMS: *m/e* 518.205 303 calcd for $C_{29}H_{30}N_2O_7$, 518.2052 found. IR (CCl_4): 2995 (w), 1770, 1445, 1370 cm^{-1}.

(±)-*anti*-*N*-((*tert*-Butoxycarbonyl)(diethylphosphono)methyl)-2-(2-oxo-4,5-diphenyloxazolinyl)-3-hydroxy-7-heptenamide (25). The same procedure for producing **23** was followed, using carboxylic acid **22** (2.20 mmol, 835 mg) in 19.5 mL of CH_2Cl_2, *tert*-butyl aminodiethylphosphonoacetate (**16**) (617 mg, 1.05 equiv), and EEDQ (816 mg, 1.5 equiv). The crude product was purified by radial chromatography (2% IPA in hexanes) to give 96% (1.330 g, 2.12 mmol) of dipeptide **25**. R_f = 0.74 and 0.77 for two diastereomers (20% IPA in hexanes), R_f = 0.12 (40% EtOAc in hexanes).

^{1}H NMR: δ 1.35 (6 H, m), 1.49 and 1.52 (9 H, 2s*), 1.5 (2 H, m), 2.2 (2 H, m), 3.88 (1 H, d, J = 8.7 Hz), and* 3.90 (1 H, d, J = 8.7 Hz), 4.19 (4 H, m), 4.65 (1 H, m), 4.98 (2 H, m), 5.08 (1 H, d, J uncertain; overlaps multiplet at δ 4.97) and* 5.15 (1 H, d, J = 9 Hz), 5.8 (1 H, m), 7.4 (10 H, m), 8.37 (0.5 H, dd, J = 2.7, 8.4 Hz), 8.53 (0.5 H, d, J = 8.4 Hz). ^{13}C NMR: δ 14.2, 16.06, 16.09, 24.9, 27.6, 28.77, 28.80, 32.90, 33.30, 50.5, 50.7, 60.4, 61.402, 61.43, 63.41, 63.47, 63.50, 63.55, 63.80, 63.87, 63.97, 67.87, 68.05, 83.17, 83.36, 83.43, 114.82, 114.88, 123.72, 124.11, 124.44, 124.48, 126.00, 126.21, 127.15, 127.32, 127.54, 127.69, 128.13, 128.20, 128.88, 129.48, 130.22, 130.26, 130.78, 134.92, 137.56, 153.99, 154.24, 164.62, 164.88, 167.87. HRMS: *m/e* 628.254 971 calcd for $C_{32}H_{41}N_2O_9P$, 628.2550 found. IR (CCl_4): 3300, 2980, 1770, 1745, 1500, 1260, 1155, 1025 cm^{-1}.

*Signals correspond to two diastereomers.

(±)-*N*-((*tert*-Butoxycarbonyl)(diethylphosphono)methyl)-3-(2-oxo-4,5-diphenyloxazolinyl)-4-(4-butenyl)azetidin-2-one (26). The procedure for preparing **24** was followed, using a solution of dipeptide **25** (1.23 g, 1.96 mmol) in 37 mL of dry THF, triphenylphosphine (2.0 equiv, 1.027 g) in 10 mL of THF, and DBAD (901 mg, 2.0 equiv) in 10 mL of THF. Purification of the crude product by radial chromatography (2% IPA in hexanes) gave a yield of 77% (918 mg, 1.50 mmol) of **26** as an oil, which by NMR still had a minor aromatic impurity. Attempted crystallization was unsuccessful. R_f = 0.77 (20% IPA in hexanes), R_f = 0.44 (10% IPA in hexanes).

^{1}H NMR: δ 1.31 (3 H, d of t, J_{HP} = 1.5 Hz, J_{HH} = 7.2 Hz), 1.39 (3 H, d of t, J_{HP} = 2.1 Hz, J_{HH} = 7.2 Hz), 1.48 and* 1.52 (9 H, 2s*), 2.16 (3 H imp, m), 2.18 and 2.41 (1 H, 2m), 4.2 (4 H, m), 4.35 (1 H, m), 4.76 (1 H, d, J = 5.4 Hz), 5.0 (3 H, m), 5.8 (1 H, m), 7.5 (18 H w/imp, m). ^{13}C NMR: δ 14.19, 16.27, 16.35, 16.46, 27.33, 27.86, 27.93, 28.29, 29.95, 31.21, 51.66, 52.88, 53.66, 54.82, 60.13, 60.28, 60.69, 61.08, 63.36, 63.44, 63.52, 63.58, 63.62, 63.67, 63.71, 83.88, 84.22, 115.61, 122.83, 124.58, 126.07, 127.26, 127.29, 128.13, 128.15, 128.39, 128.55, 129.82, 129.90, 130.64, 131.90, 131.94, 131.96, 132.09, 133.24, 135.56, 135.64, 136.97, 137.04, 153.56, 153.65, 163.80, 163.86, 164.12, 164.17, 164.34, 164.43. HRMS: *m/e* 610.244 406 calcd for $C_{32}H_{39}N_2O_8P$, 610.2440 found. IR (CCl_4): 2995, 1770, 1740, 1370, 1260, 1150, 1020 cm^{-1}.

*Signals correspond to two diastereomers.

(±)-1-Aza-3-benzamido-8-(*tert*-butoxycarbonyl)-2-oxobicyclo[4.2.0]oct-7-ene (32). A solution of β-lactam **26** (57 mg, 93.9 μmol) in 1.0 mL of dry CH_2Cl_2 was added to 30 mL of CH_2Cl_2 and cooled to −78 °C. A solution of Sudan IV indicator (61 μM; 5 μL, 71.9 μg dye content) in CH_2Cl_2 was added to produce a deep pink color. The mixture was ozonolyzed until the color had nearly faded (less than 2 min). The solution was purged with argon for 20 min, and then Me_2S (21 μL, 3 equiv) was added. The solution was allowed to reach room temperature while stirring overnight. Et_3N (12 μL, 1.0 equiv) was added, and the mixture was again stirred overnight. The crude product was passed through a 2-cm layer of silica in a Pasteur pipet, and the solvent was removed in vacuo. The yield of the carbacephem as a yellow oil was 19% (6 mg, 18 μmol). R_f = 0.35 (40% EtOAc in hexanes).

^{1}H NMR (300 MHz, 500 MHz): δ 1.50 (9 H, s), 2.01 (2 H, m, decoupling C_6 (δ 3.93) reveals dd, J = 5.5, 11.4 Hz), 2.36 (2 H, dd of AB_q, $\Delta\delta_{AB}$ = 79 Hz, J_{AB} = 20 Hz, J = 5–6.5, 5.5 Hz, upfield proton doubled again, J = 2.5 Hz), 3.93, (1 H, ddd, J = 5.7, 11.4 Hz, third J undetermined), 5.52 (1 H, dd, J = 5.4, 5.7 Hz), 6.35 (1 H, dd, J = 5.4, 2.7 Hz), 6.9–7.9 (6 H total, m and d, $J_{doublet}$ = 5.5 Hz). ^{13}C NMR (75.6 MHz): δ 20.49, 21.69, 27.93, 52.99, 59.80, 82.28, 124.56, 127.42, 128.36, 128.44, 128.62, 128.95, 129.03, 129.92, 130.13, 132.08, 132.31, 132.95, 133.51, 134.87, 160.72, 165.36, 167.83. CIMS (isobutane): *m/e* 343 (M + H). IR (thin film): 1760, 1725, 1670 cm^{-1}.

Acknowledgment. We thank Mr. Allen Ritter for performing 500-MHz NMR spectra and Mr. Don Schifferl for assistance with ^{31}P NMR spectra. We also acknowledge Dr. Bruce Plashko for mass spectral analyses. We are grateful to Eli Lilly and Co. and the NIH for providing partial financial support of this work. B.T.L. wishes to acknowledge financial support from the University of Notre Dame in the form of Nieuwland and Reilly Fellowships.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.