Table V. Partition Coefficients for 6-STC and 5a-epi-6-STC in the $CHCl_3$-H_2O System

6-STC		5a-epi-6-STC	
pH	K_D[a]	pH	K_D[a]
7	28.0	7	30.8
6	>50[b]	6	>50
5	>50	5	12.0

[a] K_D = (concentration in $CHCl_3$)/(concentration in H_2O). [b] The lipophilicity of the thiatetracycline was so high that accurate determination of the concentration in the aqueous phase was not practical.

Table VI. Intramolecular Hydrogen Bonding in the Thiatetracyclines[a]

	6-STC(0)	5a-epi-6-STC(0)	11a-OH-12a-DOH-6-STC(0)
O(2am)-H(3)	1.48 (3)	0.79 (7)	0.98 (3)
O(3)-H(3)	0.99 (3)	1.65 (6)	1.55 (3)
O(2am)-H(3)-O(3)	158 (3)	171 (9)	150 (3)
O(2am) · · · O(3)	2.431 (1)	2.427 (3)	2.450 (2)
O(10)-H(10)	0.86 (3)	0.82 (5)	0.84 (3)
O(11)-H(10)	1.74 (3)	1.89 (5)	1.82 (3)
O(10)-H(10)-O(11)	152 (3)	144 (5)	146 (3)
O(10) · · · O(11)	2.534 (1)	2.598 (4)	2.559 (2)
O(12)-H(12)	0.87 (2)	0.72 (5)	
O(11)-H(12)	1.68 (2)	1.85 (5)	
O(11)-H(10)-O(12)	152 (2)	155 (5)	
O(11) · · · O(12)	2.494 (1)	2.523 (3)	
O(12)-H(12)			0.97 (3)
O(1)-H(12)			1.56 (3)
O(12)-H(12)-O(1)			158 (3)
O(12) · · · O(1)			2.488 (2)
N(2am)-H(21)	0.86 (2)	0.77 (5)	0.92 (3)
O(1)-H(21)	2.03 (2)	2.12 (4)	1.97 (2)
O(1)-H(21)-N(2am)	137 (2)	136 (4)	133 (2)
O(1) · · · N(2am)	2.717 (1)	2.726 (5)	2.681 (2)

[a] Distances in angstroms, angles in degrees.

The enol moiety of the tricarbonylmethane system is of considerable interest not only because it sustains a central role in the equilibrium between the two forms of the free base but also because it presents an unusually short intramolecular hydrogen bond. We have reported examples where the hydrogen atom was found to be primarily associated with atom O(3)[4-6] and others in which it was localized primarily on atom O(2am).[1,16] Emphasis should be placed on the word primarily, since in an unusually short hydrogen bond the hydrogen atom is expected to bind to either oxygen atom with nearly equivalent bond energy. Difference electron density plots[19] for the appropriate region of the A ring are presented in Figure 2 for 6-STC(0) and 5a-epi-6-STC(0). These plots provide indications of partial, but not equivalent, occupancy for the hydrogen atom on each oxygen of the enol. Comparison of the appropriate C-O bond distances in Table III supports the validity of the plotted electron density. The intramolecular hydrogen-bonding geometry of the three thiatetracyclines is presented in Table VI. It is clear from Tables III and VI that the extension of the A-ring chromophore in 11a-OH-12a-DOH-6-STC(0) has not altered the hydrogen-bonding character of the A-ring enol significantly.

The extension of the A-ring chromophore in the 11a-hydroxyl derivative results in the carbonyl group at C(1) being part of an enolic β-diketone in which this group serves as an acceptor in two intramolecular hydrogen bonds. The observed carbonyl C-O bond distance closely resembles that at C(11) in the tetracyclines with the usual BCD chromophore.[7] In 11a-OH-12a-DOH-6-STC(0), the carbonyl group at C(11) also reflects the change in chemical structure. It is shortened significantly when compared with the usual value[7] but is very similar to that in 5a,11a-DH-7-ClTC(0)[1] in which the carbonyl group serves as an acceptor in only one hydrogen bond, that from the phenolic hydroxyl group. These observations and the general trend in bond distances from the high-resolution crystal structure determinations demonstrate that the tetracyclines display a high degree of integrity in their bonding geometry.

Acknowledgment. We thank the Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität Stuttgart for making this research possible.

Supplementary Material Available: Anisotropic temperature factors for the C, N, O, and S atoms, fractional atomic coordinates and isotropic temperature factors for the H atoms, bond angles between C, N, and O atoms, and calculated and observed structure factors for each structure (111 pages). Ordering information is given on any current masthead page.

(19) Program JIMPLAN, an oblique-plane Fourier plotting program in which the slant-plane Fourier transform routine of van de Waal has been incorporated by Hansen.

Synthesis of β-Lactams from Substituted Hydroxamic Acids

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Abstract: An efficient biomimetic β-lactam synthesis has been developed on the basis of cyclization of substituted β-hydroxyhydroxamic acids. The method is experimentally simple and, by appropriate choice of amino acid starting material, allows complete control of the stereochemistry at all positions of the β-lactam. The method is also compatible with the incorporation of sensitive peripheral functionality required for potential elaboration to biologically useful β-lactam derivatives. The key to the process is the low N-H pK of the intermediate *O*-alkylhydroxamic acid which facilitates diethylazodicarboxylate-triphenylphosphine (DEAD/Ph_3P) or $Ph_3P/CCl_4/Et_3N$ mediated N-C_4 bond closure to *N*-alkoxy-2-azetidinones. The sequential reduction of the latter by H_2/Pd-C followed by N-O cleavage with $TiCl_3$ leads to N-unsubstituted β-lactams.

The β-lactam antibiotics are the most widely used antimicrobial agents. However, the bacterial development of β-lactamase enzymes[1] which render some of the antibiotics ineffective has prompted a persistent search for modified antibiotic forms. While

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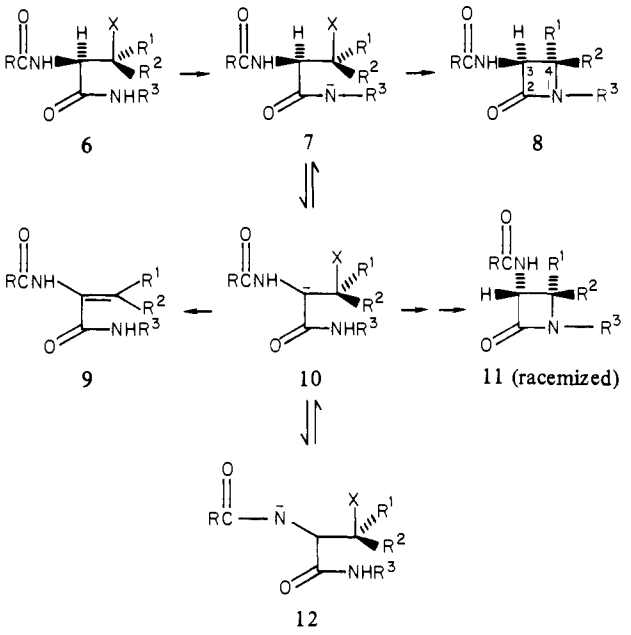
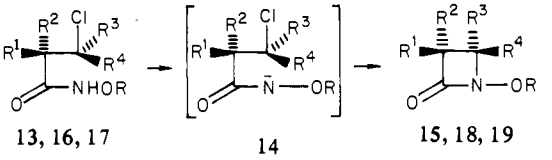
Scheme I

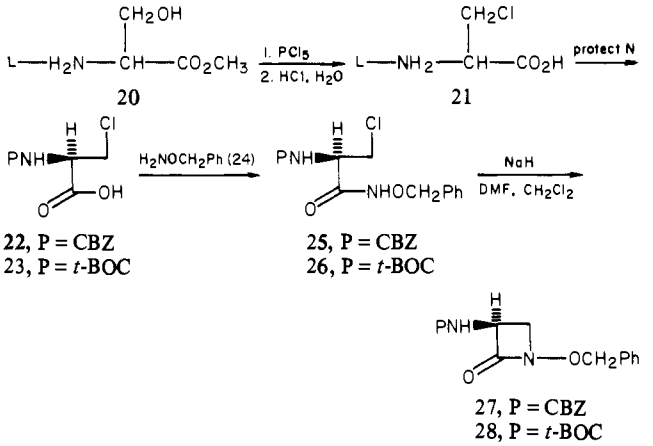


Scheme II



16, 18, R = CH_2Ph, $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$
17, 19, R = $COC(CH_3)_2$, $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$

Scheme III. Chiral Models

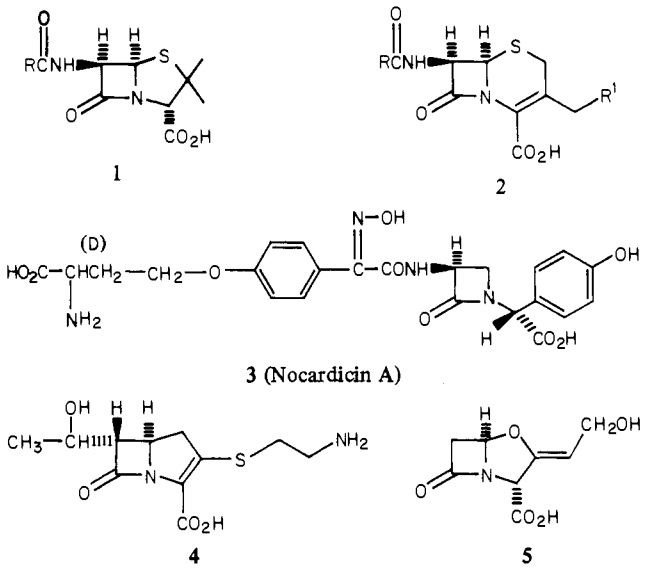


22, P = CBZ
23, P = *t*-BOC

25, P = CBZ
26, P = *t*-BOC

27, P = CBZ
28, P = *t*-BOC

traditionally most modifications have been derived from peripheral changes on the penicillins **1** and cephalosporins **2**, the recent discovery and structural elucidation of the nocardicins (**3**),[2] thienamycin (**4**),[3] clavulanic acid (**5**),[4] and others indicate that



3 (Nocardicin A)

compounds structurally quite diverse from the normal penicillins and cephalosporins might be effective antibiotics or β-lactamase inhibitors. Such structural variety has made apparent the need for an efficient synthesis of the core 2-azetidinone ring in a manner compatible with complete control and versatile incorporation of chirality and peripheral functionality. Of the many methods available for β-lactam synthesis, no single method is generally applicable to the variety of synthetic targets now being approached. Described here is the development of an efficient and versatile synthesis of β-lactams on the basis of the cyclization of substituted β-hydroxyhydroxamic acids.[5]

Synthesis of the 2-azetidinone ring system by N–C_4 bond closure (Scheme I, **7** → **8**) is especially attractive because of its biosynthetic analogy and the conceptual ability to use chiral amino acid derivatives as starting materials. Indeed, several elegant biomimetic β-lactam syntheses have been devised.[6-9] However, the required protection of the peripheral amino acid functionality and chirality, the need for a multistep incorporation of a β-leaving group, and the use of strong base in the cyclization steps decrease their utility. Ideally a biomimetic β-lactam synthesis should proceed by direct cyclization without the need for elaborate prior manipulations. While conceptually such a process is represented in Scheme I (**6** → **8**), experimentally it is not feasible. The similarity of the p*K* values of the ultimate C_3–H and the peripheral N–H bonds would lead to detrimental proton transfers and subsequent reactions with little desired cyclization. The problem, therefore, became one of differentiating the p*K* values at the three potentially ionizable positions to allow selective ionization to **7**.

Models

Cyclization of β-Chlorohydroxamates. The NH bonds of *O*-acyl- and *O*-alkylhydroxamic acids have p*K* values of 6–10,[10,11] yet the corresponding anions can be alkylated inter-[12] or intramolecularly[13] without competitive Lossen rearrangement.[11] Although such intermolecular alkylations often give mixtures of N- or O-alkylation products,[12] the preparation of substituted *N*-alkoxy

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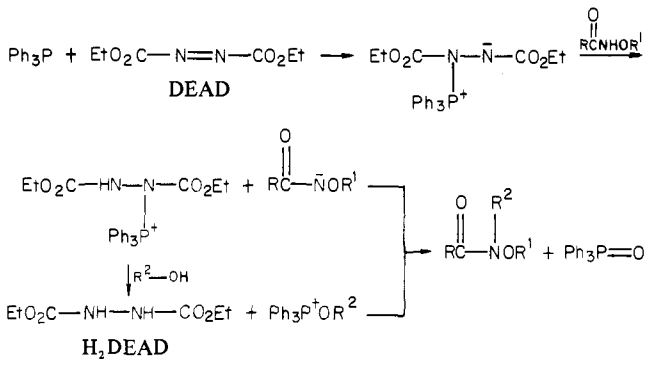
Scheme IV

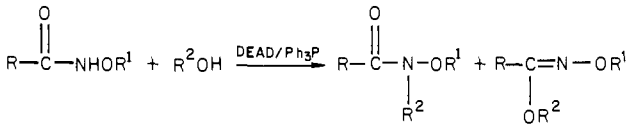


analogues **13** of the β-lactam precursor **6** was anticipated to allow selective NH ionization to **14** (Scheme II). That such mildly formed anions would be nucleophilic enough to displace a β-leaving group and form a four-membered ring had apparently been demonstrated by the reaction of 2,2-dialkyl-3-bromo acid chlorides with *O*-alkylhydroxylamines in pyridine at 70–100 °C which afforded *N*-alkoxy-3,3-dialkyl-2-azetidinones (**15**) ($R^3 = R^4 = H$).[13] However, under these conditions, whether the ring formation resulted from acylation then $N-C_4$ bond closure (**14** → **15**) or alkylation at the β position followed by $N-C_2$ bond formation was not clear. In order to test the effectiveness of an $N-C_4$ closure, we synthesized model compounds **16** and **17** by reaction of the corresponding β-chloro acids with *O*-benzylhydroxylamine and *O*-pivaloylhydroxylamine, respectively, in DMF/H_2O (1:4) at pH 4–4.5 with a water-soluble carbodiimide. The prdoucts generally precipitated from the reaction mixture. Both compounds cyclized readily (**16** → **18**, NaH, DMF, 20 °C, 1 h, 94%; **17** → **19**, Li_2CO_3, DMF, 20 °C, 24 h, 76%).

These results encouraged the synthesis of chiral models to test the differentiation of the hydroxamate nitrogen anion and potential anions at C_3 or side-chain amide. β-Chloro-L-alanine hydroxamates were considered appropriate models since intermolecular displacement reactions on β-chloro-L-alanine derivatives with benzylmercaptan ($pK = 9.4$)[14] have previously been used to prepare *S*-benzyl-L-cysteine derivatives without racemization.[15] The *N*-CBZ- and *N*-*t*-BOC-β-chloro-L-alanine *O*-benzylhydroxamates **25** and **26** were prepared by the procedure outlined in Scheme III. Thus, L-serine methyl ester (**20**) was treated with PCl_5 followed by hydrolysis to give β-chloro-L-alanine (**21**).[16] Reaction with carbobenzoxy chloride ((CBZ)Cl) gave **22** ($[\alpha]^{20}_D = +23.8°$, as the dicyclohexylammonium salt). The *t*-BOC derivative **23** ($[\alpha]^{20}_D = +22.9°$) was prepared by reaction of **21** with di-*tert*-butyl dicarbonate.[17] Carbodiimide mediated coupling of **22** and **23** with *O*-benzylhydroxylamine (**24**) in aqueous solvent gave the desired optically active hydroxamates **25** ($[\alpha]_D = -32.4°$) and **26** ($[\alpha]_D = -43.8°$) essentially quantitatively. Base-initiated cyclization provided the lactams **27** (74–86%, $[\alpha]^{20}_D = -9 \pm 3°$) and **28** (75–88%, $[\alpha]^{20}_D = -3.3 \pm 0.05°$) as anticipated. Although **27** and **28** had optical rotations, the possibility of partial racemization was not completely excluded at this point. However, no dehydrohalogenation products were detected, and stopping the reaction before completion allowed recovery of starting material with complete retention of optical activity.

Direct Cyclization of β-Hydroxyhydroxamates. With the facility of the cyclization process demonstrated, a more convenient process which would avoid the prior preparation of intermediate β-chloro-L-alanine derivatives was sought. Needed was a method of converting the β-hydroxy group of a serine hydroxamate to a good leaving group while simultaneously forming the desired nitrogen anion to initiate cyclization. Because of the nucleophilicity of the hydroxamate nitrogen, classical hydroxyl modification methods such as tosylation were not anticipated to be effective. However, the combination of triphenylphosphine (Ph_3P) and diethyl azodicarboxylate (DEAD) has mediated the alkylation of several acidic groups (carboxylic acids, phenols, imides, and others) with alcohols.[18] The only apparent limitation of this reaction is that the acidic component should have a $pK \leq 13$. Since, as previously indicated, the N–H bonds of the O-substituted hydroxamates fulfill this criterion, a mechanism based on literature analogy for other systems could be written for the $DEAD/Ph_3P$ alkylation of substituted hydroxamates with alcohols (Scheme IV).

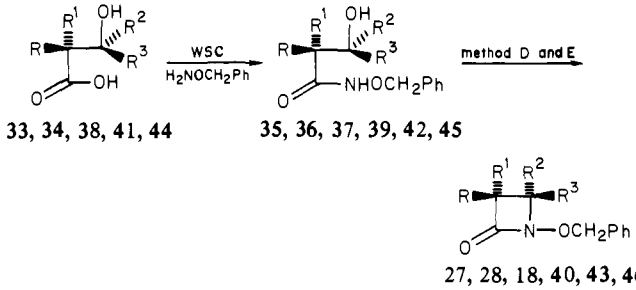
Table I. Intermolecular Alkylations of Substituted Hydroxamic Acids



R	R^1	R^2	T, °C	time, h	% *N*-alkyl[a]	% *O*-alkyl[a]	% yield
Ph	COPh	CH_2Ph	25	20	65	35	82
Ph	COPh	CH_3	50	6	76	24	88
Ph	CO_2CH_2Ph	CH_2Ph	25	20	63	37	51
CH_3	COPh	CH_2Ph	25	20	78	22	62
$(CH_3)_2CH$	CH_2Ph	CH_2Ph	25	20	100	0	66
$(CH_3)_2CH$	CH_2Ph	CH_2Ph	50	6	100	0	71
Ph	CH_2Ph	CH_2Ph	25	20	100	0	91
Ph	CH_2Ph	CH_3	25	20	100	0	67

[a] The relative percent of *N*- and *O*-alkylated isomers was determined by NMR analysis and comparison with the literature chemical shift values.[12]

Scheme V



33, 34, 38, 41, 44 **35, 36, 37, 39, 42, 45**

27, 28, 18, 40, 43, 46

initial reactant	R	R^1	R^2	R^3	first product	method[a]	second product
33	(CBZ)NH	H	H	H	35	D	27
34	(BOC)NH	H	H	H	36	D/E	28
	CH_3	CH_3	H	H	37	D/E	18
38	(BOC)NH	H	CH_3	H	39	D/E	40
41	(CBZ)NH	H	H	CH_3	42	D/E	43
44	(BOC)NH	H	H	CH_3	45	D	46

[a] Method D = $DEAD/Ph_3P$; E = $Ph_3P/CCl_4/Et_3N$.

The alkylation process was tested intermolecularly with several different alcohols and hydroxamic acids (Table I). The results indicated that while *O*-acylhydroxamates ($pK = 6–7$) gave typical mixtures of N- or O-alkylation products, the less acidic ($pK = 9–10$) *O*-alkylhydroxamates gave only the desired *N*-alkyl products. An extension, the attempted intermolecular alkylation of either *O*-benzoyl- or *O*-benzylbenzohydroxamic acids **29** or **30** with *N*-CBZ-L-serine benzyl esters (**31**), gave only the dehydroalanine elimination product **32** (eq 1).[19] While this apparent inability of intermolecular alkylation to compete with β-elimination was disappointing, we rationalized that the cyclization reaction still might proceed. Formation of an intramolecular nitrogen anion

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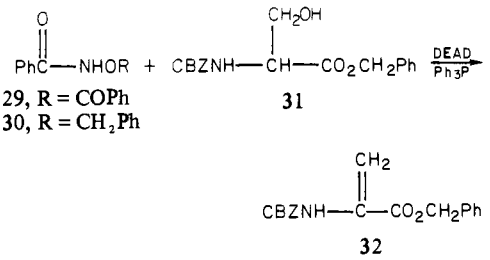


29, R = COPh
30, R = CH_2Ph

32

was anticipated to decrease the acidity of the α-C–H bond and thereby discourage elimination. Thus, *N*-CBZ- and *N*-*t*-BOC-L-serine (**33** and **34**) were each converted to the corresponding hydroxamates **35** (carbodiimide, H_2NOCH_2Ph; DMF/H_2O (1:4); pH 4.5; <30 min; 89%) and **36** (80–90%). No serine hydroxyl group protection was required for this reaction. The products usually precipitated from the aqueous reaction mixture. Treatment of **35** and **36** directly with DEAD/Ph_3P followed by chromatography and recrystallization afforded the lactams **27** and **28** in 54–82% and 80–90% yields, respectively (Scheme V). These compounds were identical in all respects, including optical rotation, with those produced from chlorides **25** and **26**. Again no elimination product (dehydroalanine) was detected. As anticipated the 3,3-dimethyl-*N*-(benzyloxy)-2-azetidinone (**18**) could also be prepared by cyclization of the corresponding alcohol **37**. Thus a versatile and efficient synthesis of *N*-alkoxy-3-substituted-2-azetidinone derivatives was demonstrated.

Extensions

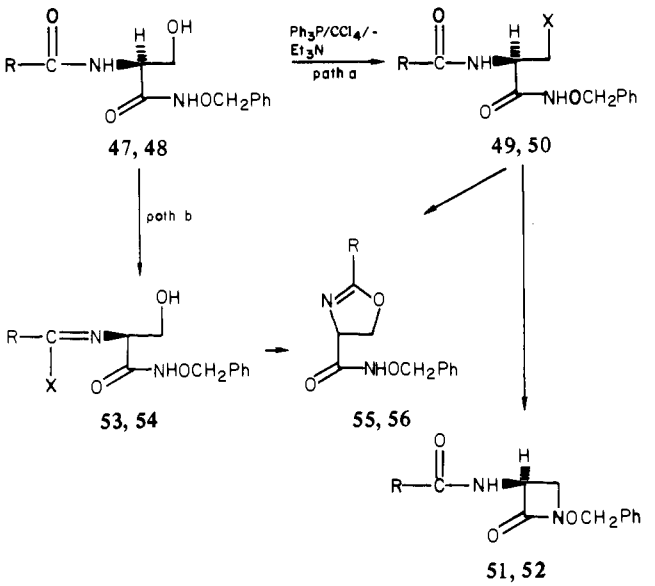
For the described methodology to be broadly applicable to the synthesis of β-lactam antibiotics, especially carbobicyclic derivatives related to thienamycin, several other features were desired. Paramount among these were (a) incorporation of substituents at C_4 in a straightforward and stereochemically controlled manner, (b) further simplification of the experimental procedure by avoiding the use of diethyl azodicarboxylate (DEAD) because the reduced form is often difficult to chromatographically separate from the substituted *N*-(benzyloxy)-2-azetidinones, and (c) efficient N–O reduction to allow subsequent elaboration at the β-lactam nitrogen by available methodology.

The amino acid, threonine, was the obvious choice of starting material to test whether the methodology would allow stereochemical control at both C_3 and C_4 of the eventual β-lactam. Thus, by the usual procedure, *N*-*t*-BOC-L-threonine (**38L**) was converted in one step to the *O*-benzylhydroxamate (**39L**). Treatment of **39L** with Ph_3P (105 mol %) and DEAD (100 mol %) in THF followed by evaporation of solvent gave a crude product which by ^1H NMR contained a mixture of starting material **39L** and product **40L** (1:5). Chromatography gave a 67% yield of **40L** as a single diastereomer. No products corresponding to racemization and/or β elimination were detected. The NMR data ($J_{C_3H-C_4H} \leq 1.5$ Hz)[20] indicated that, as expected, the trans isomer of **40L** was formed by clean inversion at the β position during cyclization. Similar results were obtained with the D-threonine derivative **38D** → **40D**. As anticipated, conversion of the D,L-*allo*-threonine derivatives **41** and **44** to the corresponding hydroxamates **42** and **45** followed by cyclization gave the cis ($J_{C_3H-C_4H}$ = 4.5–6 Hz) compounds **43** and **46**. Thus control of stereochemistry at both chiral centers of the 2-azetidinone ring has been demonstrated.

For nearly every cyclization attempted, the NMR spectrum of the crude reaction product indicated essentially quantitative conversion. However, chromatographically isolated yields were usually lower (40–90%) due to the difficult separation of the diethyl hydrazodicarboxylate (H_2DEAD) obtained from the reduction of DEAD. Thus, several DEAD analogues (dibenzyl azodicarboxylate, azodicarbonamide, and 4-phenyl-1,2,4-triazoline-3,5-dione) were tested, but these derivatives gave either no improved separation capabilities or less efficient cyclization. Combinations of triphenylphosphine and halogen sources have been used extensively to convert alcohols to halides,[21] β-amino alcohols to aziridines (with inversion),[22] and even 1-(arylamino)-3-alkanols to *N*-arylazetidines.[23] Thus analogous treatment of β-hydroxy-*O*-benzylhydroxamates was also anticipated to provide the corresponding *N*-(benzyloxy)-2-azetidinones. Reaction of *O*-benzyl-2,2-dimethyl-3-hydroxypropanohydroxamate (**37**) with Ph_3P (100 mol %), CCl_4 (100 mol %), and Et_3N (150 mol %) in CH_3CN for 20 h at room temperature under a dry nitrogen atmosphere gave a 94% yield of the desired cyclized product **18** (Scheme V) after evaporation of solvent and silica gel chromatography. In the absence of Et_3N, **18** was not formed, but the corresponding chloride **16** (16%), the starting material **37** (26.5%), and very polar uncharacterized materials were obtained. With use of the basic conditions (Ph_3P, CCl_4, Et_3N, 9–20 h, 20 °C) to preform the hydroxamate nitrogen anion, the corresponding serine and threonine hydroxamates **36** and **39** were cyclized to **28** and **40** cleanly in 78% and 86% isolated yields, respectively. The physical, spectroscopic, and optical rotatory properties of **28** and **40** so obtained were identical with those observed earlier from products obtained from the Ph_3P/DEAD mediated cyclizations. Again the threonine hydroxamates **39D** and **39L** cyclized with retention of configuration at C_3 and clean inversion at C_4. The relative ease of chromatographic separation of $Ph_3P{=}O$ from the cyclized products greatly simplified the process and resulted in higher isolated yields.

All the studies described above involved preparation of either 3,3-dialkyl-2-azetidinones or 3-amino derivatives in which the amino group was protected as a carbamate. A further test of the generality of the process involved the cyclization of other derivatives which directly provide 3-acylamino analogues with incorporation of acyl groups common in the β-lactam antibiotics. Thus, *N*-(phenylacetyl)-L-serine *O*-benzylhydroxamate (**47**) was prepared from (phenylacetyl)-L-serine by the usual carbodiimide procedure. Cyclization of **47** with $Ph_3P/CCl_4/Et_3N$ provided the lactam **51** in only 41.5% isolated yield. However, also isolated was the oxazoline **55** in 47% yield (Scheme VI). Treatment of *N*-benzoyl-L-serine *O*-benzylhydroxamate (**48**) under the same cyclization conditions ($Ph_3P/CCl_4/Et_3N$) gave a 1:4 ratio of the

Scheme VI



X = Cl or O–P^+Ph_3

47, 49, 51, 53, 55, R = CH_2Ph
48, 50, 52, 54, 56, R = Ph

(20) See the Experimental Section.

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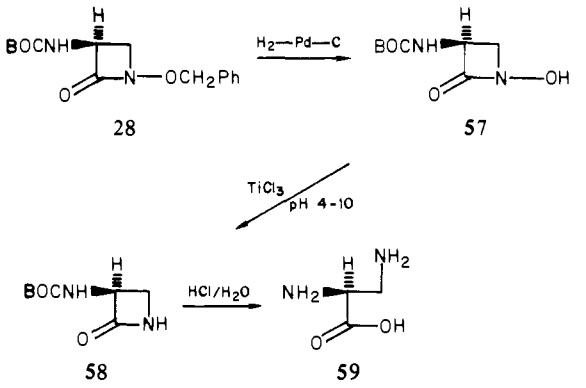
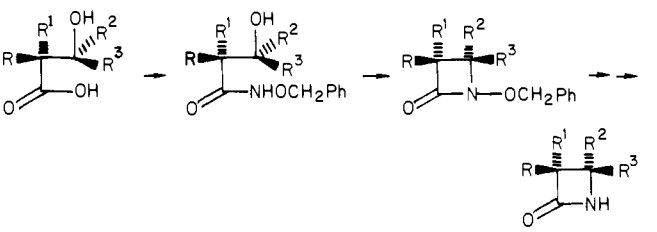
Scheme VII



Scheme VIII



β-lactam **52** and oxazoline **56**. Oxazoline formation conceivably could occur by two paths (a or b of Scheme VI). If path b were occurring not only would oxazoline be expected from hydroxyl attack at the imine of **53** and **54** but also products from competitive hydroxamate nitrogen attack of the activated agent (X) or the imines might be observed. Since no products other than β-lactam and oxazoline were observed, path a was considered more likely. If path a was, in fact, operative, the competitive nucleophilicity of the amide oxygen and hydroxamate nitrogen should be dependent on the degree of ionization of the hydroxamate nitrogen. As indicated earlier, no cyclization products were obtained if the Ph_3P/CCl_4 mixture was used without base (Et_3N). Since Et_3N and the hydroxamate nitrogen have similar pK values, complete hydroxamate nitrogen ionization may not have been effected with this base. Considering again that the apparent pK of the Ph_3P/DEAD adduct is near 13, the cyclization of the phenylacetyl derivative **47** with Ph_3P/DEAD as the mediator was attempted with the anticipation that less reversible hydroxamate nitrogen anion formation should increase the relative amount of β-lactam formed. Indeed, the β-lactam **51** was obtained in 63% yield after chromatography and recrystallization while only a 10–20% yield of the oxazoline **55** was observed in the crude reaction mixture. Fortunately, the 3-aminoacyl derivatives such as **51** and **52** were readily separated chromatographically from H_2DEAD. Although not eliminated by the use of DEAD/Ph_3P, the detrimental oxazoline formation was minimized and the utility of the desired cyclization procedure expanded.

Thus, a facile synthesis of substituted *N*-hydroxy-2-azetidinones with versatile incorporation of peripheral functionality and control of stereochemistry at both C_3 and C_4 was demonstrated. However, in order to allow elaboration to N-substituted monocyclic or bicyclic β-lactams, an efficient method of N–O reduction was requried. Many methods of N–O reduction have been described. Application of several of these methods to the desired reduction gave either no reaction or undesired ring opening. As previously reported,[24] however, the sequential reduction of the *O*-benzylhydroxamates (i.e., **28**) with H_2–Pd/C (CH_3OH, 1 atm, 0.5–1 h) to the *N*-hydroxy compounds **57** followed by treatment with buffered $TiCl_3$ allows efficient reduction to the N-unsubstituted β-lactams **58** in a manner compatible with acid-sensitive functionality (*t*-BOC) and base-sensitive chiral centers (Scheme VII). Acidic hydrolysis of **58** provided optically pure L-2,3-diaminopropionic acid **59**,[25] thereby confirming the assigned structure and the retention of optical activity during the synthesis.

Conclusion

In summary (Scheme VIII), an efficient biomimetic β-lactam synthesis has been developed on the basis of cyclization of substituted β-hydroxyhydroxamic acids. The methodology is experimentally simple and allows complete control of stereochemistry on the β-lactam while remaining compatible with the incorporation of sensitive peripheral functionality. Thus, the process should be readily applicable to the synthesis of both monocyclic and bicyclic β-lactam derivatives of biological interest. Such extensions are being studied.

Experimental Section

General Comments. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Infracord and 727B spectrometers. NMR spectra were determined in chloroform-*d* with tetramethylsilane as a reference, unless otherwise indicated, by using Varian A-60A or XL 100 spectrometer. Mass spectra were recorded on an AEI Scientific Apparatus MS 902 or DuPont DP 102 spectrometer. Elemental analyses were performed by Midwest Microlabs. Experiments performed at constant pH utilized a Metrohm CD 3 combititrator-pH Stat. The cyclization reactions required dry solvents which were prepared by recommended procedures.[26]

***N*-CBZ-β-chloro-L-alanine (22)** was prepared from β-chloro-L-alanine (**21**) and isolated as the dicyclohexylammonium salt according to literature procedures:[27] mp 155–158 °C (lit.[27] mp 155 °C); $[\alpha]^{20}_D$ +23.8° (c = 2.5, DMF), lit.[32] $[\alpha]^{20}_D$ +24.3° (c = 2.5, DMF).

***N*-*t*-BOC-β-chloro-L-alanine (23)**. Di-*tert*-butyl dicarbonate[17] (2 g, Aldrich) and 2.54 mL (18.4 mmol) of triethylamine were added to a solution of 1.47 g (9.2 mmol) of β-chloro-L-alanine (**21**)[27] in 25 mL of DMF at room temperature. A precipitate (Et_3N·HCl) formed immediately. The mixture was stirred overnight then poured into 50 mL of ethyl acetate. The suspension was extracted with two 25-mL portions of water and two 25-mL portions of 5% $NaHCO_3$. The combined aqueous layers were carefully acidified to pH 2.5–3.0 with solid citric acid and then extracted with three 30-mL portions of ethyl acetate. The combined ethyl acetate from this latter extraction was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give a thick oil. Chromatography on silica gel with ethyl acetate followed by recrystallization from ethyl acetate/hexanes gave 860 mg (45%) of **23**: mp 123–125 °C; $[\alpha]^{20}_D$ +22.9 (c = 2, CH_3OH); NMR ($CDCl_3$) δ 1.48 (s, 9 H), 4.0 (m, 2 H), 4.75 (m, 1 H), 5.7 (br d, NH), 11.5 (br s, ca. 2 H).

***N*-*t*-BOC-D-Threonine (38D)**. D-threonine (2.96 g, 24.9 mmol, Sigma) was added to 70 mL of DMF–H_2O (1:6). Triethylamine (3.5 mL) and di-*tert*-butyl dicarbonate (6.5 g, 120 mol %, Aldrich) were added, and the reaction was stirred at room temperature for 1 day. The mixture was then acidified to pH 3 with 1 N HCl and extracted with four 30-mL portions of ethyl acetate. The combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$, filtered, and evaporated to give **38D** as a crude oil. NMR ($CDCl_3$): δ 1.24 (d, 3 H), 1.48 (s, 9 H), 4.27 (m, 3 H), 5.9 (d, 1 H), 8.37 (br s, 1 H). The oil was dissolved in ether, and 100 mol % of dicyclohexylamine (DCHA) was added. A white precipitate began to form within minutes and was filtered off 3 h later to yield 4.65 g (47% yield overall) of the DCHA salt of **38D**, mp 153.5–154 °C (lit.[28] mp for L isomer 153.5–154.5 °C).

Anal. Calcd for $C_{21}H_{40}N_2O_5$: C, 62.97; H, 10.07; N, 6.99. Found: C, 63.17; H, 10.22; N, 7.28.

***N*-CBZ-D,L-*allo*-threonine (41)**. D,L-*allo*-Threonine (974 mg, 8.2 mmol, ICN Pharmaceuticals) and $NaHCO_3$ (3 g, 400 mol %) were dissolved in 15 mL of H_2O. Benzyl chloroformate (1.83 g, 10.8 mmol, 125 mol %) was added over a 3-min period. The reaction was stirred vigorously for 1.5 h and then extracted with two 25-mL portions of ether. The aqueous layer (pH 8) was then acidified to pH 2 with 1.2 N HCl and immediately extracted with four 25-mL portions of ether. These latter organic extracts were combined, washed with 15 mL of brine, and dried over $MgSO_4$. Filtration and concentration yielded 1.91 g (7.55 mmol, 92%) of a clear oil. NMR ($CDCl_3$): δ 1.2 (d, 3 H), 3.9–4.6 (m, 2 H), 5.07 (s, 2 H), 6.2 (br s, OH, NH, and CO_2H), 7.3 (s, 5 H). A portion of the oil was dissolved in ether containing 1 equiv of dicyclohexylamine. The dicyclohexylammonium salt of **41** precipitated (mp 152–153 °C).

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Anal. Calcd for $C_{24}H_{38}N_2O_5$: C, 66.33; H, 8.81; N, 6.45. Found: C, 66.48; H, 9.08; N, 7.13.

***N*-*t*-BOC-D,L-*allo*-threonine (44)** was prepared in 76% yield from D,L-*allo*-threonine (ICN) with the di-*tert*-butyl dicarbonate procedure[17] used for **23**, mp 174–176 °C (lit.[29] mp 175–176.5 °C).

***N*-(Phenylacetyl)-L-serine (47)** was prepared in 69% yield by reaction of L-serine with a suspension of phenylacetyl chloride in aqueous Na_2CO_3. Recrystallization from ethyl acetate/hexanes gave **47** with a melting point of 95–97.5 °C. Recrystallization from H_2O gave **47** as the hemihydrate, mp 75–78 °C (lit.[30] mp 74–75 °C).

***N*-Benzoyl-L-serine (48)** was prepared in 74% yield by reaction of L-serine with a suspension of benzoyl chloride in aqueous K_2CO_3. Recrystallization from acetone, including a hot filtration to remove a trace of insoluble material, gave **48**, mp 148–150 °C (lit.[31] mp 148–149 °C).

Formation of the Hydroxamic Acids: the Coupling Reaction. Two methods were employed. **Method A** was similar to that reported earlier.[11] Thus, a solution containing the carboxylic acid (0.05–0.1 M) in H_2O, THF/H_2O, or DMF/H_2O, depending on the solubility of the carboxylic acid and 1–1.5 equiv of either (*O*-benzylhydroxyl)amine (OBHA, Aldrich) or (*O*-pivaloylhydroxyl)amine (OPHA)[11] was adjusted to pH 4–5 and an aqueous solution of the water-soluble carbodiimide (WSC, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride, Sigma) was added. The pH was maintained at 4–5 either by addition of 1 N HCl manually or with a pH stat. The coupling reaction was usually complete in less than 30 min, and when no cosolvent (THF, DMF) was used, the products often precipitated. If the product oiled out or remained soluble, the reaction mixture was extracted with three protions of ethyl acetate. The combined ethyl acetate was washed with two portions of 1 N citric acid, two portions of 5% $NaHCO_3$ (more basic extractions often removed the product), H_2O, and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed or directly recrystallized from ethyl acetate–hexanes.

Method B was similar to method A but used the less expensive but water-insoluble dicyclohexylcarbodiimide (DCC). Consequently, mixed solvents (THF/H_2O) were used, and the DCC was added as a solution in THF. The products were crudely separated from contaminating dicyclohexylurea by washing the filtered precipitates with ethyl acetate. The ethyl acetate portions were then concentrated and the residue chromatographed on silica gel or directly crystallized.

***O*-Benzyl-β-chloropivalohydroxamate (16)** was prepared from β-chloropivalic acid (Aldrich) and OBHA by method A in 77% yield: mp 90–91.5 °C (recrystallized from ethyl acetate/hexanes); NMR ($CDCl_3$) δ 1.25 (s, 6 H), 3.61 (s, 2 H), 5.95 (s, 2 H), 7.44 (s, 5 H), 8.67 (br s, NH).

***O*-Pivaloyl-β-chloropivalohydroxamate (17)** was prepared from β-chloropivalic acid (Aldrich) and OPHA by method A in 88% yield: mp 137–137.5 °C; NMR ($CDCl_3$) δ 1.35 (s, 9 H), 1.4 (s, 6 H), 3.73 (s, 2 H), 9.4 (s, NH).

Anal. Calcd for $C_{10}H_{18}O_3NCl$: C, 50.96; H, 7.70; N, 5.94. Found: C, 50.70; H, 7.68; N, 5.85.

***O*-Benzyl-*N*-CBZ-β-chloro-L-alanine hydroxamate (25)** was prepared from **22** and OBHA in 96% yield by method A: mp 146.5–148.5 °C; NMR ($CDCl_3$) δ 3.75 (d, 2 H, br), 4.6 (m, 1 H), 4.9 (s, 2 H), 5.1 (s, 2 H), 5.95 (d, br NH), 7.39 (s, 5 H), 7.41 (s, 5 H), 9.6 (s, br NH); $[\alpha]^{20}_D$ −32.4° (c = 2, CH_3OH).

Anal. Calcd for $C_{18}H_{19}O_4N_2Cl$: C, 59.59; H, 5.28; N, 7.72; Cl, 9.77. Found: C, 59.73; H, 4.99; N, 7.84; Cl, 10.10.

***O*-Benzyl-*N*-*t*-BOC-β-chloro-L-alanine hydroxamate (26)** was prepared by method A from **23** and OBHA in 98% crude yield and 83% recrystallized yield (ether/hexanes): mp 89.5–92 °C; $[\alpha]^{20}_D$ −43.8° (c = 2.2, CH_3OH); NMR ($CDCl_3$) δ 1.45 (s, 9 H), 3.8 (br d, 2 H), 4.5 (m, 1 H), 4.93 (s, 2 H), 5.5 (br d, NH), 7.44 (s, 5 H), 9.45 (br s, NH); mass spectrum (CI with CH_4), m/e 329 (M + 1).

***O*-Benzyl-α-*N*-CBZ-L-serine hydroxamate (35)** was prepared from *N*-CBZ-L-serine (**33**, Sigma) and OBHA by method A in 89% yield: mp 125–127 °C; NMR ($CDCl_3/CD_3COCD_3$; 1:1) δ 3.7–4.4 (m, 4 H, α-C*H*, β-CH_2, OH), 4.9 (s, 2 H), 5.1 (s, 2 H), 6.1 (br d, 1 H), 7.35 (s, 10 H), 10.5 (br s, 1 H); $[\alpha]^{20}_D$ −25.9° (c = 3.2, CH_3OH).

***O*-Benzyl-α-*N*-*t*-BOC-L-serine hydroxamate (36)** was prepared from *N*-*t*-BOC-L-serine (**34**, Sigma) and OBHA by method A in 80–90% yields and method B in 79.5% yield: mp 130–131 °C; NMR ($CDCl_3$) δ 1.45 (s, 9 H), 3.65–4.67 (br m, 4 H), 4.95 (s, 2 H), 5.85 (d, 1 H), 7.43 (s, 5 H), 8.05 (br s, 1 H); IR (KBr) 1650 cm^{-1} (C=O); mass spectrum (CI with CH_4), m/e 311 (M + 1); $[\alpha]^{20}_D$ −37.7° (c = 1.94, CH_3OH).

Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.06; H, 6.77; N, 9.03. Found: C, 57.90; H, 7.00; N, 9.01.

***O*-Benzyl-2,2-dimethyl-3-hydroxypropano hydroxamate (37)** was prepared from 2,2-dimethyl-3-hydroxypropionic acid and OBHA by method A in 87% yield: mp 81.5–83 °C; NMR ($CDCl_3$) δ 1.3 (s, 6 H), 3.1 (br s, 1 H), 3.5 (s, 2 H), 4.9 (s, 2 H), 7.42 (s, 5 H), 9.42 (s, 1 H); IR (KBr) 1640 cm^{-1} (C=O); mass spectrum, m/e 223.

***O*-Benzyl-α-*N*-*t*-BOC-D-threonine hydroxamate (39D)** was prepared from α-*N*-*t*-BOC-D-threonine (**38D**) (as the dicyclohexylammonium salt) and OBHA by method A in 47% yield: mp 92.5–93.5 °C; NMR ($CDCl_3$) δ 1.15 (d, 3 H), 1.46 (s, 9 H), 3.6–4.3 (br m, 3 H), 4.92 (s, 2 H), 5.77 (d, 1 H), 7.4 (s, 5 H), 9.7 (br s, 1 H); IR (KBr) 1680 cm^{-1}; mass spectrum (CI with CH_4) m/e 325 (M + 1).

Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.25; H, 7.46; N, 8.64. Found: C, 59.03; H, 7.46; N, 8.91.

***O*-Benzyl-α-*N*-*t*-BOC-L-threonine hydroxamate (39L)** was prepared from *N*-*t*-BOC-L-threonine (**38L**) (Chemical Dynamics) and OBHA by method A in 51% yield: mp 91–94 °C; NMR ($CDCl_3$) identical with **39D**; IR identical with **39D**; $[\alpha]^{20}_D$ +37.1° (c = 1.5, CH_3OH).

Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.25; H, 7.46; N, 8.64. Found: C, 59.37; H, 7.39; N, 8.89.

***O*-Benzyl-α-*N*-CBZ-D,L-*allo*-threonine hydroxamate (42)** was prepared from *N*-CBZ-D,L-*allo*-threonine (**41**) and OBHA by method A in 69% yield: mp 154.5–156 °C; NMR ($CDCl_3$) δ 1.12 (d, 3 H), 3.7–4.15 (br, 2 H), 4.85 (s, 2 H), 5.05 (s, 2 H), 5.2–5.7 (br, 1 H), 5.9–6.2 (br d, 1 H), 7.35 (s, 10 H), 9.5 (br s, 1 H); IR ($CHCl_3$) 1700 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.68; H, 6.19; N, 7.82. Found: C, 63.28; H, 6.07; N, 7.78.

***O*-Benzyl-α-*N*-*t*-BOC-D,L-*allo*-threonine hydroxamate (45)** was prepared from *N*-*t*-BOC-D,L-*allo*-threonine (**44**) and OBHA by method A in 76% yield: mp 132–134 °C; NMR ($CDCl_3$) δ 1.24 (d, 3 H), 1.47 (s, 9 H), 3.3–4.0 (m, 3 H, α-CH, β-CH, OH), 4.93 (s, 2 H), 5.5 (br, NH), 7.43 (s, 5 H), 8.33 (s br, NH).

Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.00; H, 7.50; N, 8.79.

***O*-Benzyl-α-*N*-(phenylacetyl)-L-serine hydroxamate (49)** was prepared by method A from *N*-(phenylacetyl)-L-serine **47** and OBHA in 67% yield: mp 153–155 °C; NMR (Me_2SO-d_6) δ 3.3–3.7 (m, 2 H), 3.54 (s, 2 H), 4.83 (s, 2 H), 4.9 (br s, 1 H), 7.32 (s, 5 H), 7.42 (s, 5 H), 8.2 (d, NH), 11.2 (s, NH); IR (KBr) 1630 cm^{-1}; $[\alpha]^{20}_D$ −44° ± 3° (c = 2.15, CH_3OH).

***O*-Benzyl-α-*N*-benzoyl-L-serine hydroxamate (50)** was prepared from *N*-benzoyl-L-serine (**48**) and OBHA in 58% yield (recrystallized from acetone): mp 181–182 °C; NMR (Me_2SO-d_6) δ 3.36 (s, OH), 3.75 (br t, 2 H), 4.5 (m, 1 H), 4.88 (s, 2 H), 7.3–7.65 (m, 8 H; with s, 5 H at 7.45), 7.85–8.1 (m, 2 H), 8.35 (d, NH), 11.15 (s, NH).

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.98; H, 6.00; N, 8.72.

Cyclization Reactions: Formation of the 2-Azetidinone Ring. Three methods were employed. **Method C** involved base (NaH or Li_2CO_3) initiated cyclization of O-substituted β-chlorohydroxamates. Thus, the β-chlorohydroxamate dissolved in DMF or THF was added to a suspension of 100 mol % of Li_2CO_3 (for *O*-acylhydroxamates) or NaH (prewashed with hexanes; for *O*-alkylhydroxamates) in the same solvent at room temperature. The reaction was followed by TLC of a neutralized aliquot. Upon disappearance of starting material, the reaction mixture was poured into water, neutralized with 1 N HCl, and extracted with three portions of ether or ethyl acetate. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and evaporated. The product was either recrystallized from ethyl acetate–hexanes or distilled at reduced pressure.

Method D involved the cyclization of substituted β-hydroxyhydroxamates with Ph_3P/DEAD. Thus, the β-hydroxyhydroxamate was dissolved in a THF solution containing 100 mol % of Ph_3P. The concentration of substrate in all cases was ≤0.2 M. While being stirred under N_2 or a $CaCl_2$ drying tube, a solution of diethylazodicarboxylate (DEAD, Aldrich, 100 mol %) in THF was added by the drop or by syringe. After the addition was complete, the reaction was monitored for disappearance of starting material by TLC. Upon completion (1–20 h at room temperature, less time at 50 °C), the solvent was removed under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate/hexanes to separate the product from reduced DEAD and Ph_3PO. Recrystallization from ethyl acetate–hexanes gave the analytical materials.

Method E is essentially the same as method D except that CCl_4 and Et_3N were used instead of DEAD. The workup was identical with that above, but the chromatography was much simpler (essentially a filtration to remove Ph_3PO).

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N-(Benzyloxy)-3,3-dimethyl-2-azetidinone (18) was prepared from the chloride **16** in 94% yield by method C (DMF, NaH, 1 h): bp 95 °C (0.1mmHg); mp ca. 20 °C; NMR ($CDCl_3$) δ 1.2 (s, 6 H), 3.08 (s, 2 H), 4.95 (s, 2 H), 7.45 (s, 2 H); IR (neat film) 1780 cm^{-1}; mass spectrum (CI with CH_4), m/e 206 (M + 1).

Compound **18** was also prepared by methods D and E in 99% and 94% yields, respectively, from the β-hydroxyhydroxamate (**37**).

N-(Pivaloyloxy)-3,3-dimethyl-2-azetidinone (19) was prepared in 76% yield from chloride **17** by method C (DMF, Li_2CO_3, 24 h): mp 42.5–43.5 °C; NMR ($CDCl_3$) δ 1.28 (s, 9 H), 1.40 (s, 6 H), 3.54 (s, 2 H); IR 1770 cm^{-1}.

3-[(CBZ)amino]-1-(benzyloxy)-2-azetidinone (27) was prepared in 74–86% yields from chloride **25** by method C [DMF/CH_2Cl_2 (1:1), NaH, 50 °C, 12 h] and in 83% chromatographed (63% recrystallized) yield by method D: mp 89.5–91 °C.; NMR ($CDCl_3$) δ 3.25 (dd, 1 H, J = 2.5 Hz), 3.50 (t, 1 H, J = 5 Hz), 4.4–4.65 (m, 1 H), 4.93 (s, 2 H), 5.08 (s, 2 H), 5.95 (br d, NH), 7.33 (s, 5 H), 7.38 (s, 5 H); IR (KBr) 1770 cm^{-1}; mass spectrum (CI with CH_4), 327 (M + 1); $[\alpha]^{20}_D$ −9° ± 3° (c = 2, CH_3OH).

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.59. Found: C, 65.93; H, 5.60; N, 8.64.

3-[(t-BOC)amino]-1-(benzyloxy)-2-azetidinone (28) was prepared in 75–88% yield from chloride **26** by method C (DMF/CH_2Cl_2 (1:1), 50 °C, 12 h), in 62% yield by method D, and in 86% yield by method E: mp 91.5–92 °C; NMR ($CDCl_3$) δ 1.41 (s, 9 H), 3.18–3.33 (dd, 1 H), 3.55 (t, 1 H), 4.33–4.5 (m, 1 H), 5.0 (s, 2 H), 5.13–5.47 (m, 1 H), 7.48 (s, 5 H); IR (KBr) 1700, 1760, 3310 cm^{-1}; mass spectrum (CI with CH_4), m/e 293 (M + 1); $[\alpha]^{20}_D$ = −3.9 (C = 2.65, CH_3OH).

Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.64; H, 6.85; N, 9.59. Found: C, 61.35; H, 6.80; N, 9.49.

3-[(t-BOC)amino]-1-(benzyloxy)-4-methyl-2-azetidinone (40D) was prepared from **39D** by method E in 79% yield: mp 75–75.5 °C; NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 7 Hz), 1.45 (s, 9 H), 3.55 (dq 1 H, when decoupled from the methyl at δ 1.25, the doublet of quartets collapsed to a doublet with J = 1.5 Hz), 4.05 (br d, 1 H), 5.0 (s, 2 H), 5.35 (br d, 1 H), 7.46 (s, 5 H); IR ($CHCl_3$) 1780, 1720 cm^{-1}; mass spectrum (CI with CH_4), 307 (M + 1).

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 63.00; H, 7.51; N, 9.22.

The enantiomer **40L** was prepared from **39L** by methods D and E in 67% and 75% yields, respectively: mp 76.3–77 °C; $[\alpha]^{20}_D$ −49.6 ± 0.3° (c = 1.5, CH_3OH); NMR and IR identical with that of **40D**.

The isomer **46** was prepared from the *allo*-threonine derived hydroxamate **45** in 89.7% yield by method D: mp 137.5–139 °C; NMR ($CDCl_3$) δ 1.07 (d, 3 H, J = 6.5 Hz), 1.44 (s, 9 H), 3.8 (m, 1 H, collapsed to a d, J = 4.5 Hz, upon decoupling the peak at δ 1.07), 4.7 (m, 1 H, collapsed to a d, J = 4.5 Hz, upon decoupling the carbamate NH at 5.2), 4.9 (s, 2 H), 5.2 (br d, NH), 7.45 (s, 5 H).

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.92; H, 7.33; N, 9.28.

3-[(CBZ)amino]-1-(benzyloxy)-4-methyl-2-azetidinone (43) was prepared from **42** by method D in 66% yield: mp 114.5–115 °C; NMR ($CDCl_3$) δ 1.02 (d, 3 H), 3.78 (m, 1 H), 4.72 (dd, 1 H, J = 8, J = 2 Hz), 4.95 (s, 2 H), 5.11 (s, 2 H), 6.09 (br d, NH), 7.35 (s, 5 H), 7.42 (s, 5 H); IR ($CHCl_3$) 1778, 1720 cm^{-1}.

1-(Benzyloxy)-3-(phenylacetamido)-2-azetidinone (51) was prepared from the hydroxamate **49** by methods D and E. After evaporation of solvent, the crude reaction mixtures were chromatographed on silica gel with ethyl acetate/hexanes (1:1). Two major products were obtained, the β-lactam **51** [R_f = 0.45, silica gel, ethyl acetate/hexanes (3:1)] and the **oxazoline 55** (R_f = 0.3). From method D, lactam **51** was obtained in 60–63% yield: mp 127.5–129 °C; NMR ($CDCl_3$) δ 3.16 (dd, 1 H), 3.54 (s, 2 H superimposed on t, 1 H), 4.65 (m, 1 H), 4.95 (s, 2 H), 6.92 (br d, NH), 7.42 (s, 5 H), 7.4 (s, 5 H); IR ($CHCl_3$) 1780, 1680 cm^{-1}; $[\alpha]^{20}_D$ +9.1 (c = 2.2, CH_3OH).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.86; N, 9.03. Found: C, 69.64; H, 5.79; N, 8.91.

Method D also provided **oxazoline 55** in 10–20% yield: NMR ($CDCl_3$) δ 3.52 (s, 2 H), 4.42 (m, 3 H; appears as a br s, 2 H, superimposed on t, 1 H), 4.88 (s, 2 H), 7.27 (s, 5 H), 7.37 (s, 5 H), 9.7 (br s, NH); IR ($CHCl_3$) 1690, 1658 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.86; N, 9.03. Found: C, 70.02; H, 5.99; N, 8.91.

Method E provided lactam **51** in 41.5% yield and oxazoline **55** in 47% yield.

1-(Benzyloxy)-3-benzamido-2-azetidinone (52) (22%) and **oxazoline 56** (73%) were formed from hydroxamate **50** under the conditions of method E. Chromatography on a tlc grade silica gel column at 100 psi and 6 mL/min with 20% ethyl acetate in hexanes was required to separate β-lactam **52** and oxazoline **56**. Compound **52**: mp 120–121.5 °C; NMR ($CDCl_3$) δ 3.35 (dd, 1 H), 3.8 (t, 1 H, J = 5 Hz), 4.9 (m, 1 H), 5.0 (s, 2 H), 7.46 (s, 5 H; superimposed on 7.3–7.95 m, 5 H).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 69.11; H, 5.59; N, 9.43.

Compound **56**: mp 124.5–126.5 °C; NMR ($CDCl_3$) δ 4.7 (m, 3 H; appears as a s, 2 H, superimposed on a t, 1 H), 4.95 (s, 2 H), 7.47 (s, 5 H), 7.4–8.0 (m, 5 H), 9.65 (br s, NH).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.63; H, 5.55; N, 9.31.

3-[(t-BOC)amino]-1-hydroxy-2-azetidinone (57), **3-[(t-BOC)amino]-2-azetidinone (58)**, and the hydrolysis of **58** to **L-2,3-diaminopropionic acid (59)** have been previously described.[24]

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