(M^+, 100), 190 (54), 162 (32), 108 (50), 84 (34); high-resolution mass spectrum, *m/e* 191.1318 ($C_{12}H_{17}NO$ requires 191.1310).

Acknowledgment. We thank the National Science Foundation (CHE 8106040A1) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 3a, 77413-79-7; **3b**, 77413-80-0; **3c**, 87842-62-4; **3d**, 87842-63-5; **3e**, 77413-82-2; **3f**, 87842-64-6; **5**, 7340-09-2; **6**, 87842-65-7; **7**, 87842-66-8; (±)-**9**, 87842-67-9; (±)-**10**, 62279-67-8; **12**, 77413-86-6; **13**, 87842-68-0; **14**, 87842-69-1; **16**, 87842-70-4; **17**, 87842-71-5; **18**, 87842-72-6; **20**, 87842-73-7; **21**, 87842-74-8; **24**, 87842-75-9; **25**, 87842-76-0; **28**, 87842-77-1; **30**, 87842-78-2; **31**, 87842-79-3; 4-pentenoyl chloride, 39716-58-0; 1,2,3,8,9,9a-hexahydro-4-quinolizinone, 87842-80-6; *cis*-1,7,8,8a-tetrahydro-8-phenyl-3(2*H*)-indolizinone, 77413-85-5; 1,7,8,8a-tetrahydro-2-oxa-3(2*H*)-indolizinone, 87842-81-7; 1-azatricyclo[5.3.1.$0^{4,11}$]undec-9-en-2-one, 77413-84-4; *N*-allylacetamide, 692-33-1; *N*-allylhydroxylamine, 52716-05-9; *N*-allyl-*N*-(4-pentenoyl)hydroxylamine, 87842-83-9; *O*-acetyl-*N*-(2-butenyl)-*N*-(4-pentenoyl)hydroxylamine, 87842-84-0; 1-bromo-2-butene, 4784-77-4; *N*-(2-butenyl)-*N*,*O*-diacetylhydroxylamine, 87842-85-1; *O*-acetyl-*N*-(2-butenyl)hydroxylamine, 87842-86-2; 4-bromo-2-pentene, 1809-26-3; *N*-(2-penten-4-yl)-*N*,*O*-diacetylhydroxylamine, 87842-87-3; *O*-acetyl-*N*-(1-methyl-2-butenyl)hydroxylamine, 87842-88-4; *N*,*O*-diacetyl-*N*-(1-cyclohexenylmethyl)hydroxylamine, 87842-89-5; *O*-acetyl-*N*-(1-cyclohexenylmethyl)hydroxylamine, 87842-90-8; 1-bromomethylcyclohexene, 37677-17-1; allyl bromide, 106-95-6.

Heterocycles as Masked Diamide/Dipeptide Equivalents. Formation and Reactions of Substituted 5-(Acylamino)oxazoles as Intermediates en route to the Cyclopeptide Alkaloids

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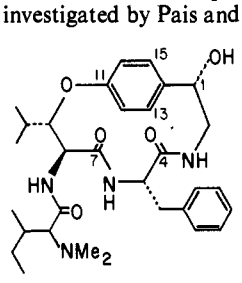
Contribution from the Department of Chemistry, University of California, Santa Barbara, California 93106. *Received April 11, 1983*

Abstract: A variety of novel 2,4-dialkyl-5-(acylamino)oxazoles have been prepared by using either amide nitriles or diamides/dipeptides as starting materials. Ring closure calls for the use of trifluoroacetic acid/trifluoroacetic acid anhydride or an acid halide in chlorinated solvents. The first examples of chiral systems have also been prepared incorporating both alkyl and protected amine substitutents at the C-2 methyl residue derived from the corresponding amino acids. Unmasking of these heteroaromatic moieties to their dipeptide equivalents is demonstrated. Both carbon and nitrogen alkylation chemistry is examined as model studies for subsequent elaboration to specific heterocyclophanes, potential precursors of numerous cyclopeptide alkaloids.

The cyclopeptide alkaloids ("phencyclopeptines") make up a rapidly expanding class of naturally occurring compounds that have been known for almost a century.[2] The first definitive structure elucidation, however, was not reported until 1966 when pandamine (**1**), was investigated by Pais and co-workers.[3] Since



1, Pandamine

this time the number of these bases isolated and of known structure continues to increase, there presently being over 80 members.[4]

Several characteristic features are common to the majority of these alkaloids. Generally they contain a 13-, 14-, or 15-membered ring, incorporating an aryl ether, which in turn is derived from a *p*-hydroxystyrylamine moiety and a *β*-hydroxyamino acid residue. A rather limited number of amino acids serve to complete the cyclic array, which tend to have hydrophobic side chains. These include phenylalanine, leucine, and isoleucine, although valine-, proline-, and tryptophane-derived species have been observed.[2]

Although the phencyclopeptines are found in the leaves and bark of a number of plants, extraction techniques usually afford highly complex mixtures containing as many as 20 components, rendering isolation of individual compounds an extremely tedious adventure.[2] From their common occurrence, however, has come a rich history of service in folk medicine. This tradition continues today among natives of central and southern Africa where natural sources of phencyclopeptines are used as remedies for diarrhea and dysentary.[2] Much of the modern medicinal interest in these cyclophanes, especially where the 14-membered ring series is concerned, stems from their potential as specific ion sequestering agents. Frangulanine (**2**) has been reported to induce swelling in rat liver mitochondria in 0.15 M KCl or RbCl solution but has no effect in aqueous solutions of NaCl or LiCl.[5] Similarly,

(1) Recipient of an American Cancer Society Junior Faculty Research Award, 1981–1983.

(2) For general reviews on the phencyclopeptines, see: (a) Bycroft, B. W.; Wels, C. M. *Amino Acids, Pept. Prot.* **1976**, *8*, 310. (b) Tschesche, R.; Kauzmann, E. U. In "The Alkaloids"; Manske, R., Ed.; Academic Press: New York, 1975; Vol. XV, p 165. (c) Pais, M., Jarreau, F.-X. In "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins"; Weinstein, B., Ed.; Marcel Dekker, New York, 1971; Vol. 1, p 127. (d) Warnhoff, E. W. *Alkaloids (London)*, **1971**, *1*, 444.

(3) Pais, M. Jaureau, F.-X., Lusinchi, X., Goutarel, R. *Ann. Chim. (Paris)*, **1966**, *13*, 83 and references therein.

(4) For some recent reports on newly characterized compounds, see: Lagarias, J. C.; Goff, D.; Klein, F. K.; Rapoport, H. *J. Nat. Prod.* **1979**, *42*, 220. Morel, A. F.; Barvo, R. V. F.; Reis, F. A. M.; Revuda, E. A. *Phytochemistry* **1979**, *18*, 473.

(5) Kawai, K.; Nozawa, Y.; Ogihara, Y. *Experientia* **1977**, *33*, 1454.

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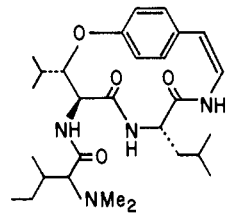


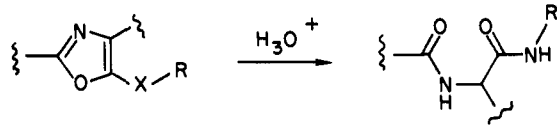
2, Frangulanine

Rapoport and co-workers[6] employed CD studies to demonstrate metal ion complexation selectivity in both a naturally occurring (Ceanothine B; Mg^{2+} and Ca^{2+} over Na^{+}) and model macrocyclic system (14-membered ring; Mg^{2+} and Ca^{2+} over Li^{+}, and K^{+}).

Only recently have efforts directed toward the total synthesis of these dipeptides been reported. In this regard, Rapoport[6] and Pais[7] have made major contributions, and Schmidt[8] has described the synthesis of dihydro analogue of both 13- and 14-membered ring systems in the zizyphine A, B, and G series. Most recently, Joullié[9] has described a very interesting four-component condensation approach to substituted prolyl peptides en route to dihydromauritine A.

In each of these studies, cyclization relies upon formation of a lactam bond, a particularly difficult task in the paracyclophane series considering the s-trans conformation of the two amide linkages. Indeed, the literature shows quite clearly that lactamization across either the 3,4 or 6,7 positions of seco derivatives not containing at least one proline residue is a highly inefficient process (0–14% yield).[6,7] Where one or more proline derivative is present the yields increase to as much as 50%.[8] Reviews[2] on the cyclopeptide alkaloids point to a need for new strategies in tackling this problem, as by far the majority of phencyclopeptines of potential biological interest are non-proline-containing molecules.

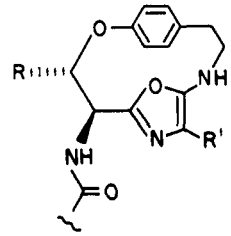
One possible route considered was to devise improved methods for ring closure. While the realization of such a goal would certainly be a contribution, we were intrigued with the possibility of encapsulating the key structural unit of these bases (i.e., the diamide or, better yet, the dipeptide) into a single new entity, 3,



3, X = NR, O

which could then be incorporated into a cyclophane network. Subsequent unmasking of 3 via perhaps a single chemical event or series of operations would lead to the desired architectural array.

Some time ago we recognized that appropriately substituted oxazoles should, in general, be susceptible to acid hydrolysis leading to carboxyl derivatives.[10] While alkyl-substituted/aryl-substituted systems are notoriously resistant to hydrolysis, the judicious placement of either an alkoxy or amine substituent at C-5 leads to the ready addition of water across the 4,5 double bond (which is formally a ketene acetal), leading to either an amide ester or diamide.[11] Should this process occur wherein an amine residue is located on the C-2 methyl moiety, a dipeptide equivalent would be in hand. Hence, the new target structure becomes oxazolophane 4, which is functionally equivalent to the desired (dihydro) ring system in the natural series.

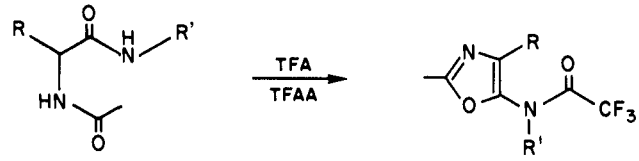


4

In this report we discuss the preparation of several new 5-(acylamino)oxazoles using two distinct routes. The first relies on cyclization of readily available α-amido nitriles while the second involves ring formation from diamides or dipeptides. These tailor-made heteroaromatics can be further functionalized by using both carbon and nitrogen alkylation chemistry, the latter of particular concern looking toward cyclophane formation via construction of the 2,3 bond (see 1). An entry into the chiral series has also been realized. Finally, we demonstrate that, indeed, an oxazole of this substitution pattern (i.e., as in 4) has the potential to serve as a dipeptide synthon, yielding its functional equivalency under extremely mild conditions.

Results and Discussion

Preparation and Reactions of 5-(Trifluoroacetamido)oxazoles from α-Acylamino Amides. The pioneering work of Fleury et al.[11,12] almost a decade ago illustrated the propensity of α-acylamino amides to undergo cyclization upon treatment with neat trifluoroacetic anhydride (TFAA) in the presence of strong acid to form 5-(trifluoroacetamido)oxazoles. While this procedure



seemed a bit costly, the trifluoroacetyl residue appeared to have merit as an amide protecting group in that it is known to undergo N-alkylation[13] and can be removed under relatively mild conditions.[14] While literature yields for closures of this type tended to be high (ca. 80–90%),[11,12] not a single derivative had been reported which did not bear an aromatic ring on the oxazole nucleus. Hence, we were somewhat skeptical about the likelihood of forming the corresponding alkyl heterocycles, especially when combined with an effort to decrease the amount of TFAA required.

In time it was discovered that excellent yields of 2,4-dialkyl-5-(trifluoroacetamido)oxazoles could be realized by using 2.5 equiv of TFAA relative to diamides 5–7 in CH_2Cl_2 at room temperature. Table I lists the oxazoles prepared in this way and attests to both the generality of this modified method and the finding that no loss in efficiency occurs with changes in either the stabilizing power of the substituents or quantity of trapping agent (i.e., TFAA) present.

With examples 8–11 (Table I) in hand, in particular entry 3 containing a benzyl group at the C-4 position which corresponds to one of the residues characteristic of the phencyclopeptides,[15] we next investigated their N-alkylation. Using a variety of bases (e.g., LiH, NaH, KH, K_2CO_3) in different solvents (THF, DMF, with and without HMPA) and temperatures (room temperature → 65 °C) in the presence of up to 10 equiv of activated electrophiles (MeI, $PhCH_2Br$, allyl bromide), we were never able to

(6) Goff, D.; Lagarias, J. C.; Shih, W. C.; Klein, M. P.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4814. Lagarias, J. C.; Houghton, R. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 8202.

(7) Rocchiccioli, F.; Jarreau, F.-X.; Pais, M. *Tetrahedron* **1978**, *34*, 2917. Frappier, F.; Rocchiccioli, F.; Jarreau, F.-X.; Pais, M. *Ibid.* **1978**, *34*, 2911 and references therein.

(8) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Talbiersky, J. *J. Org. Chem.* **1982**, *47*, 3261 and references therein.

(9) Joullié, M. M.; Nutt, R. F. *J. Am. Chem. Soc.* **1982**, *104*, 5852.

(10) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389.

(11) Clerin, D.; Kille, G.; Fleury, J.-P. *Tetrahedron* **1974**, *30*, 469.

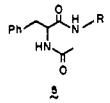
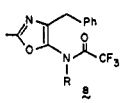
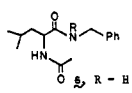
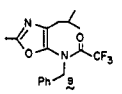
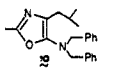
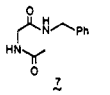
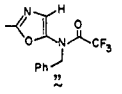
(12) (a) Clerin, D.; Fleury, J.-P. *Bull. Soc. Chim. Fr.* **1973**, 3127. (b) *Ibid.* **1973**, 3134.

(13) Gribble, G. W.; Soll, R. M. *J. Org. Chem.* **1981**, *46*, 2433.

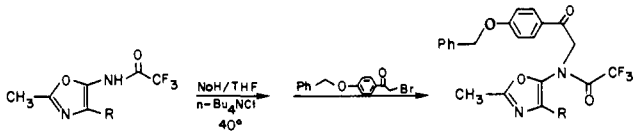
(14) Green, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981, p 254.

(15) See reference 2b.

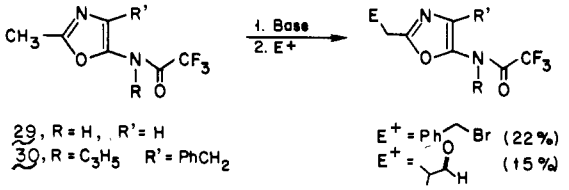
Table I. Ring Closure of Diamides to 5-(Trifluoroacetamido)oxazoles Using TFAA

Entry	α-Amide	Conditions	Product	Yield [%]
	 4		 8	
1	5, R = CH_2Ph	TFA (1.0 equiv) TFAA (2.5 equiv) CH_2Cl_2, rt, 24h	8, R = CH_2Ph	82
2	5, R = $CH_2CH=CH_2$	TFA (2.5 equiv) TFAA (10 equiv) CH_2Cl_2, rt, 24h	8, R = $CH_2CH=CH_2$	98
3	5, R = H	TFA (1.5 equiv) TFAA (2.5 equiv) $CHCl_3$, rt, 26h	8, R = H	85
4	 6, R = H	TFA (10 equiv) TFAA (2.5 equiv) CH_2Cl_2, rt, 26h	 9	92
5	5, R = CH_2Ph	TFA (3.5 equiv) 1 M in TFAA rt, 18h	 10	86
6	 7	TFA (1.5 equiv) TFAA (2.5 equiv) $CHCl_3$, rt, 26h	 11	40

realize yields of greater than 35%. Most additives (TMEDA, DMAP, 18-crown-6, $PdCl_2$) likewise were of little consequence in a positive sense. Our best conditions, NaH/THF, *n*-Bu_4NCl,[16] 40 °C, afforded modest yields of product as a function of ring susbtitution, the 4-phenyl case,[17] of little synthetic value in our scheme, consistently giving significantly higher yields (ca. 50%) than the 4-benzyl-substituted system (ca. 30%) irrespective of the nature of the electrophile.

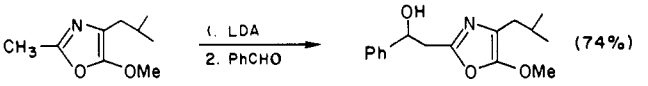


Concurrent with our N-alkylation studies we investigated metalation possibilities at C-2. Our experience with lithiations along these lines led us to try both LDA and *n*-BuLi in THF at −78 °C.[18] In the case of secondary trifluoroacetamides **29**, use



of 2 equiv of base followed by the addition of any one of several electrophiles (benzaldehyde, methyl iodide, isobutyraldehyde, benzyl bromide, Me_3SiCl) afforded unacceptably low yields (10–30%) of product. Even when N-substituted cases **30** were attempted with 1 equiv of base, 2-alkylated material was still isolated in poor yields (15–25%).

In light of our earlier work where metalation and alkylation/condensation at C-2 of 2-methyl-4,5-dialkyl/aryloxazoles was an efficient process,[18] we suspected the trifluoroacetamido group to be too electrophilic for our purposes. To confirm this we prepared 5-methoxyoxazole **31** by a literature route[19] which upon

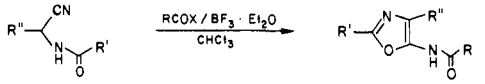


31 32

treatment with LDA and THF at −78 °C followed by benzaldehyde afforded adduct **32** in 74% isolated yield.

As a result of the complications surrounding use of the 5-(trifluoroacetamido)oxazoles in both C-2- and N-alkylations, we decided to abandon this particular derivative in favor of other acylated 5-aminooxazoles. Inspection of the literature revealed that cyclizations were mainly known to occur under conditions of H^+/TFAA.[12a,20,21] An investigation of other anhydrides was not pursued after it was found that addition of a diamide to Ac_2O (as solvent) containing TFA (1.0 equiv) at 35 °C led to none of the desired 5-acetamidooxazole, even upon prolonged reaction times (48 h). Introduction of DMAP had no effect on the reaction course.

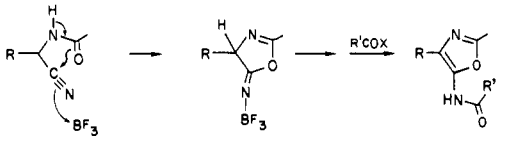
Ultimately, it was reasoned that acid halides should provide reactivity somewhat comparable to that of TFAA. Since Fleury et al.[20] have also investigated oxazole formation via α-amide nitriles **33** (using TFA/TFAA), we were delighted to find that with an



33 34

acid bromide or chloride (1.5 equiv) in the presence of $BF_3 \cdot Et_2O$ (1.0 equiv) in chlorinated solvent good yields of 5-(acylamino)-oxazoles **34** could be realized. Other Lewis (e.g., $TiCl_4$, Et_2AlCl, $SnCl_2$, $ZnCl_2$) or protic (TFA) acids were at times satisfactory; however, $BF_3 \cdot Et_2O$ seemed most convenient and consistently gave the best results, as summarized in Table II.

Clearly an assortment of C-2-, C-4-, and C-5-substituted systems can be prepared. Functionalization at C-2 may incorporate an alkyl (entries 1–3), aryl (entry 7), vinyl (entries 4–6), or protected aminoalkyl (entries 8,9) residue. C-4 was designed to contain the desired isobutyl (entries 1, 2, 8, 10) or benzyl (entries 3, 4, 6, 7, 9) moiety or may be unsubstituted (entry 5). Yields of oxazoles formed tended to be considerably higher when this position bears an alkyl group (vs. a proton). Presumably substitution at C-4 enhances the stability of both the intermediate and heteroaromatic unit ultimately formed, following intramolecular attack by amide **35** en route to **36**, as shown.



35 36

The choice of acid halide seemed not to be a severely limiting factor for cyclization. In general, acid bromides were most prone toward effecting ring closure, usually complete at 0 °C in a few hours. Acid chlorides, by contrast, called for refluxing $CHCl_3$ for up to 1 day. Interestingly, yields were not dramatically different between the two types of reagents. In certain cases problems arose in product isolation. For example, by use of $Cl_2CHCOCl$ (entry 2, Table II), the desired oxazole was isolated in 30% yield (46% based on recovered starting material), presumably due to the lability of the α-halo amide to handling and chromatography.

(16) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535. Grieco, P. A.; Majetich, G. F.; Onfune, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4226. Grieco, P. A.; Onfune, Y.; Majetich, G. F.; Wang, C.-L. *Ibid.* **1982**, *104*, 4233.

(17) Prepared by the method of Fleury et al.[20]

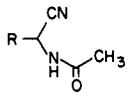
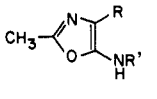
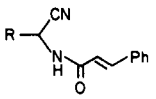
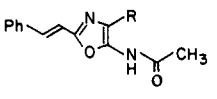
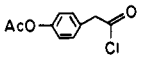
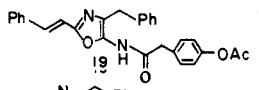
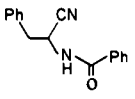
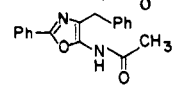
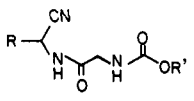
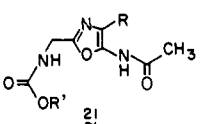
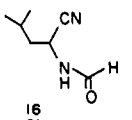
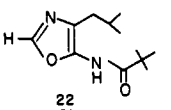
(18) Lipshutz, B. H.; Hungate, R. W. *J. Org. Chem.* **1981**, *46*, 1410.

(19) Firestone, R. A.; Harris, E. E.; Reuter, N. *J. Org. Chem.* **1966**, *27*, 2705.

(20) (a) Baysang, A.; Fleury, J.-P. *Bull. Soc. Chim. Fr.* **1969**, 4102. (b) Fleury, J.-P.; Baysang, A.; Clerin, D. *Bull. Soc. Chim. Fr.* **1969**, 4108.

(21) Sekiya, M.; Suzuki, J.; Kakiya, Y. *Chem. Pharm. Bull.* **1970**, *18*, 1233.

Table II. Conversion of α-(Acylamino)nitriles to 5-(Acylamino)oxazoles Using $BF_3 \cdot Et_2O$

Entry	α-Acylaminonitriles	Acid Halide	Conditions	Product	Yield (%)
	 12			 17	
1	12, R = $CH_2CH(CH_3)_2$	CH_3COBr	$CHCl_3$, 0°, 2 h	17 R' = $COCH_3$	70
2	12, R = $CH_2CH(CH_3)_2$	$Cl_2CHCOCl$	$CHCl_3$, rt, 18h	17, R' = $COCHCl_2$	46
3	12, R = CH_2Ph	CH_3COBr	CH_2Cl_2, rt, 4.5h	17, R' = $COCH_3$	73
	 13			 18	
4	13, R = CH_2Ph	CH_3COBr	$CHCl_3$, 0°, 1h → rt, .5h	18, R = CH_2Ph	100
5	13, R = H	CH_3COCl	CH_2Cl_2, 34°, 24h	18, R = H	70
6	13, R = CH_2Ph		$CHCl_3$, 1↓, 4h	 19	72
7	 14	CH_3COBr	CH_2Cl_2, 0°, 1h	 20	63
	 15			 21	
8	15, R = $CH_2CH(CH_3)_2$ R' = CH_3	CH_3COBr	CH_2Cl_2, 0°, 1h	21, R = $CH_2CH(CH_3)_2$ R' = CH_3	72
9	15, R = R' = CH_2Ph	CH_3COBr	$CHCl_3$, 0°, 6h	21, R = R' = CH_2Ph	69
10	 16	t-BuCOCl	$CHCl_3$, 1↓, 36h	 22	74

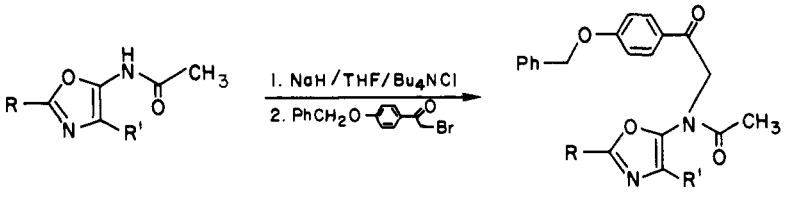
Several other examples in Table II are worthy of note. Entries 4, 5, and 6 demonstrate that vinyloxazoles, which may function as Michael acceptors, can be prepared directly by this route. Oxazole **19**, possessing all of the requisite carbon atoms, is a potential precursor to the phencyclopeptine skeleton, having been assembled in essentially a single operation. Entries 8 and 9, which contain a C-2 protected aminomethyl substituent, represent in themselves new technology as latent dipeptide equivalents (vide infra). C-2 protio oxazole **22** (entry 10) is especially valuable as it opens up the possibility for a direct metalation/condensation sequence.[22]

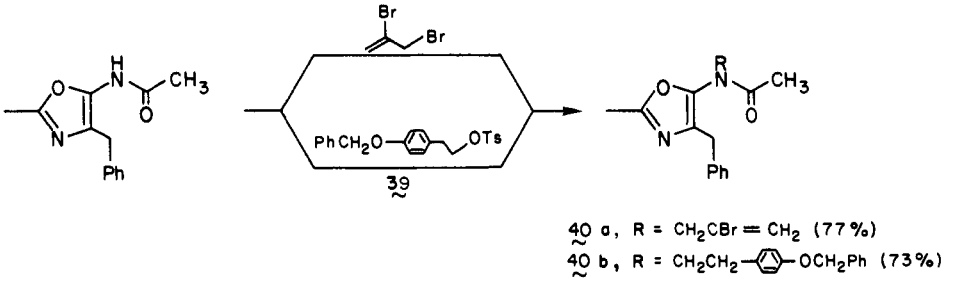
The α-amino nitriles required as precursors to 5-(acylamino)oxazoles were readily available from aldehydes following the Gaudry modification[23] of the Strecker method for synthesis of α-amino acids. A cold (ca. 5 °C) aqueous solution of KCN, to which is added sequentially NH_4Cl (1.1 equiv) and concentrated NH_4OH (5 equiv), is stirred vigorously and the aldehyde (0.96 equiv) is slowly introduced. The mixture is diluted with Et_2O and allowed to stir at ambient temperature. Simply extracting the product into Et_2O and treating the dried extracts at 0 °C with dry HCl gas afford the crystalline hydrochloride salts routinely in yields of 70–90%. In this way, quantities of up to 15 g have been prepared without loss in efficiency.

The two amine hydrochloride salts that have been used extensively in our work are those derived originally from isovaleroaldehyde and phenylacetaldehyde. The former is conveniently obtained as a white crystalline solid which begins to decompose above 160 °C (160–190 °C), while the latter is realized as a yellow solid. Trituration with hot Et_2O somewhat decolorlizes the salt producing a pale yellow amorphorous product (mp 142–157 °C dec). Both amine hydrochlories are used without any additional purification or handling.

5-(Acylamino)oxazoles via Cyclization of Diamides/Dipeptides. As discussed earlier herein, diamides are converted to 5-(trifluoroacetamido)oxazoles under the influence of TFA/TFAA. Therefore, concurrent with our investigation on ring closures of α-amide nitriles just described, we examined this alternative route to oxazoles using our modified conditions (i.e., Lewis acid/acid halide) developed for α-acylamino nitriles. The results are summarized in Table III. Formation of 5-N-substituted-acetamido derivatives proceeded quite readily (59–86%) when acetyl bromide in the presence of either $ZnBr_2$ or $ZnCl_2$ was used. Acetyl chloride gave a somewhat reduced yield (73%), as did the use of ZnI_2. Aroyl halides, in general, gave disappointingly low product yields (21–47%) regardless of the zinc halide employed. Other Lewis

(22) Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1980**, *45*, 2550.
(23) Gaudry, R. *Can. J. Chem.* **1946**, *24(B)*, 301.

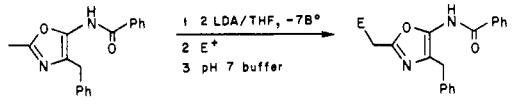




acids, including $FeCl_3$, $CaCl_2$, Me_3SiOTf, $TiCl_4$, $SnCl_4$, Et_2AlCl, as well as $BF_3{\cdot}Et_2O$, were found to be less effective than $ZnBr_2$. While the overall efficiency of this route is clearly not, in many cases, comparable with cyclization of amide nitriles, there are certain advantages to this procedure: (1) it permits the direct formation of either secondary or tertiary (acylamino)oxazoles, the latter of particular value in anticipation of a metalation/alkylation sequence at the C-2 methyl group (i.e., no dianion or N–H protecting group chemistry needed); (2) it has potentially more flexibility with regard to the conversion of known diamides/dipeptides (e.g., one containing a tryptophan residue) to 4-substituted 5-(acylamino)oxazoles; (3) it can be performed with amide esters leading to 5-alkoxyoxazoles which, following elaboration and unmasking back to the ester, can be converted to an amide of one's choosing.

The *N*-acetylamino acids were prepared from the corresponding acylated amino acids in good yields[24] (60–80%) by using a modified version of a literature report. While DCC coupling with amines worked well at times, the chromatographic problems associated with its use encouraged us to opt for the mixed anhydride route employing methyl chloroformate (1.0 equiv at −5 °C). In some instances the overall yields of amides were somewhat lower (ca. 10%) via this procedure; however, the relative ease of product isolation more than compensated for these differences (see Experimental Section).

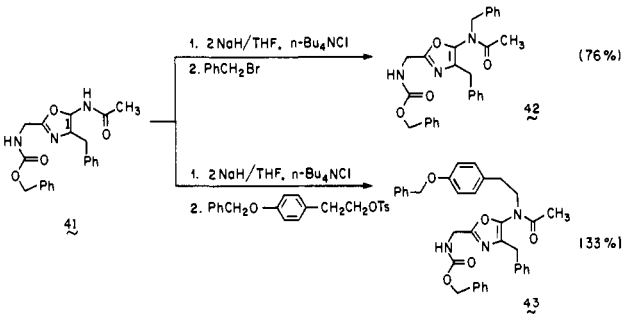
Functionalization of 5-(Acylamino)oxazoles. With two straightforward means of realizing a variety of 2,4-disubstituted (or unsubstituted) 5-(acylamino)oxazoles in hand, attention was next focused on further functionalization of the C-2 methyl group. Benzamide **37** was chosen for this purpose as formation of its



dianion, which avoids a protection/deprotection series, is clearly preferred. Again, contrary to our observations in the trifluoroacetamide case, both metalation and condensation/alkylation processes proceeded in a remarkably straightforward manner. Quenching the dianion intermediate with isobutyraldehyde led to a single product **38a** by TLC. Unfortunately, this material proved to be unstable to silica gel filtration, and hence, only a yield of ca. 70% was isolated. Addition of benzyl bromide, however, afforded the expected product (**38b**) to the extent of ca. 80%.

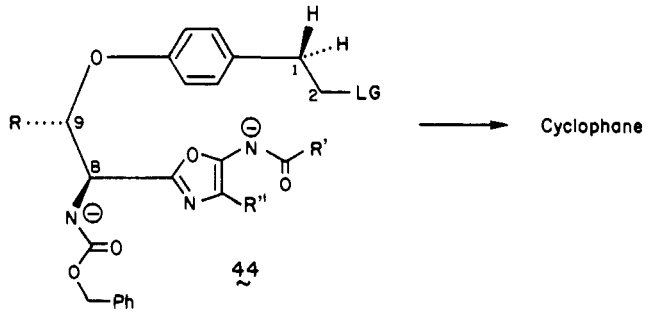
Likewise, the N-alkylation of these oxazoles proceeded smoothly in most cases at room temperature. Unactivated electrophiles, such as primary tosylate **39**, required slightly elevated temperatures (ca. 35 °C). Isolated yields in the 66–82% range were now routinely observed. It is particularly significant that the tosylate **39** of a phenethyl alcohol led to only the product of displacement without competing elimination to a styrene derivative. Furthermore, only ca. 1 equiv of electrophile is needed, suggesting that the intramolecular variation (i.e., on a secocyclophane) may be a viable route to the target oxazolophane **4**.

Somewhat more relevant cases of N-alkylation concern those oxazoles possessing a protected amine appendage at the C-2 methyl group, as in the Cbz derivative **41**. Due to the presence of acidic



protons on both the amide and urethane nitrogens, 2 equiv of base is now required. Following dianion generation, addition of 1 equiv of an activated electrophile (e.g., benzyl bromide) to the pot containing *n*-Bu_4NCl[16] (1 equiv) afforded a 76% isolated yield of product **42** derived from the *exclusive* alkylation at the amide position. This selectivity was only observed when the tetraalkylammonium salt was present which presumably leads to some of the tetrabutylammonium salt of the amide, effectively increasing its reactivity relative to the urethane anion. This process is also dependent on the nature of the electrophile, since carrying out the same reaction under otherwise identical conditions with a primary, unactivated tosylate led to the highly functionalized oxazole **43** in only 33% yield. The major byproducts resulted from elimination of the elements of TsOH to give the corresponding styrene and mixtures of mono- and dialkylated materials from competition for the electrophile by the urethane anion. While initially there was some concern about this observation, it was soon recalled that these are examples of intermolecular processes. Cyclophane formation via construction of the C-2, 3-N bond (see **1**), however, is to involve an intramolecular event which would have in place the C-8, C-9 connection, as in, e.g., **44**. Molecular models of **44** make it quite clear that the only process that should

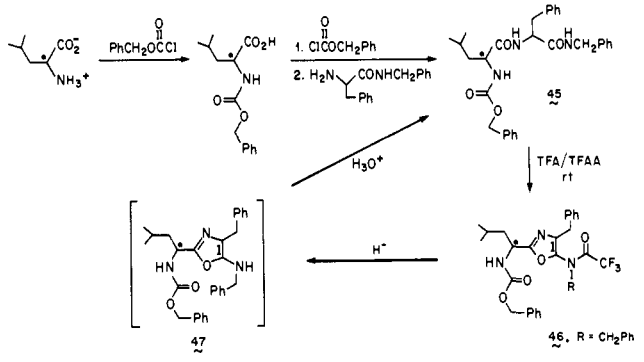
(24) Carter, H. E., *Org. React. (N.Y.)* **1946**, *3*, 198.
(25) Borello, E.; Zeahina, A.; Appiano, A. *Spectrochim. Acta* **1966**, *22*, 927.



44

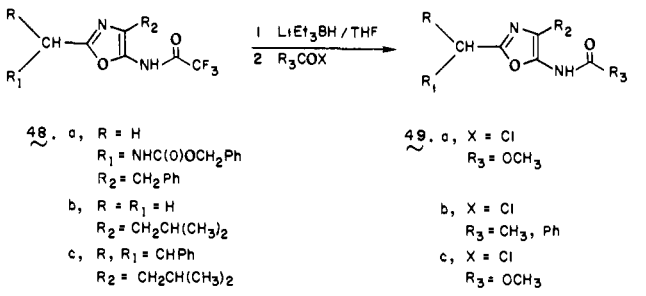
occur, presumably under high dilution conditions, is displacement at the amide site. N-Alkylation at the urethane moiety would lead to a ten-membered ring parafused across a benzene ring, a most unlikely happening. The same argument can be used to address an elimination pathway across the 1,2 positions. Furthermore, the option always exists to change the nature of the amine protecting group (e.g., $-Si(Me_2)CH_2CH_2(Me_2)Si-$)[26] such that proton abstraction is not a concern.

Preparation and Reactions of Chiral 5-(Acylamino)oxazoles. Our procedures for the construction of the 5-(acylamino)oxazole nucleus are especially amendable to the introduction of chirality into these systems. To demonstrate such an entry, we began with L-leucine and converted it to the Cbz dipeptide **45** using standard



peptide coupling techniques. Treatment of **45** with catalytic TFA containing 2.5 equiv of TFAA in CH_2Cl_2 gave oxazole **46** in 98% yield ($[\alpha]^{23}_D$ −27.1° (*c* 0.085, $CHCl_3$)). Optical purity was established by hydrogenolysis of both chiral and racemic samples of **46** with ammonium formate/palladium on carbon[27] to the corresponding free primary amines which were immediately coupled with (*S*)-(−)-Mosher's acid[28,29] (75% overall). Comparison of the NMR spectra at 80 MHz of the amides so obtained was more than sufficient to indicate, within the limits of detection, that a single enantiomer had been formed from L-leucine, as evidenced by the single quartet at δ 3.43. The oxazole originating from racemic leucine shows methyl resonances for the methoxy group at both δ 3.43 (*J* = 1.6 Hz) and 3.33 (*J* = 1.3 Hz) in the expected 1:1 ratio, also as quartets due to long-range coupling with fluorine.

In light of both the chemically and stereochemically efficient ring closure of diastereomers **45** under conditions of TFA/TFAA, the possibility of exchanging a more manageable nitrogen protecting group for the CF_3CO- residue was explored. Soluble $NaBH_4$ was found to be ineffective at cleaving secondary trifluoroacetamides. In time, Super-Hydride ($LiEt_3BH$, Aldrich)[30] was determined to be the reagent of choice, such that addition of, e.g., **48** to ca. 2 equiv of $LiEt_3BH$ in THF, initially at −78 °C

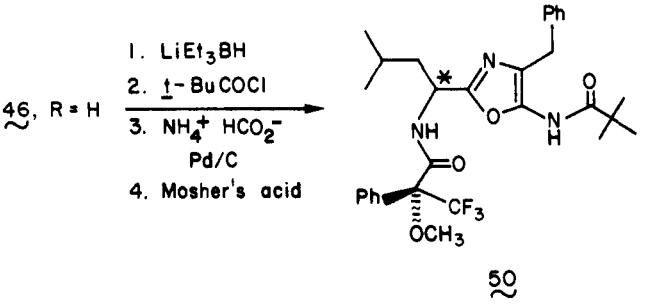


48. a, R = H
R_1 = NHC(O)OCH$_2$Ph
R_2 = CH$_2$Ph
b, R = R_1 = H
R_2 = CH$_2$CH(CH$_3$)$_2$
c, R, R_1 = CHPh
R_2 = CH$_2$CH(CH$_3$)$_2$

49. a, X = Cl
R_3 = OCH$_3$
b, X = Cl
R_3 = CH$_3$, Ph
c, X = Cl
R_3 = OCH$_3$

with eventual warming to room temperature followed by inverse addition to an acylating agent in CH_2Cl_2, afforded the amide or urethane derivatives **49** in good yields.

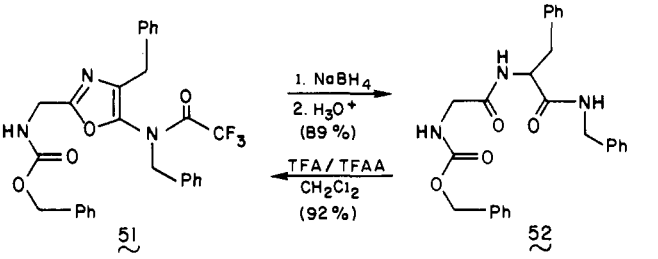
Exchange of the trifluoroacetyl moiety in chiral **46** (R = H)



50

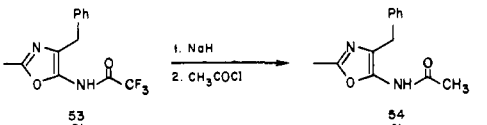
for a pivaloyl residue followed by hydrogenolysis and Mosher amidation afforded **50**. NMR analysis led to the conclusion that only one enantiomeric species was in hand. From these examples, we can suggest with some degree of confidence that chirality at C-8 (phencyclopeptine numbering) will be maintained during this important two-step sequence.[35]

Finally, to establish the viability of this approach wherein 5-(acylamino)oxazoles serve as masked dipeptides, we have prepared oxazole **51** as illustrated below. Cleavage of the trifluoroacetamide group with $NaBH_4$[31] followed by treatment with cold, dilute aqueous acetic acid afforded the Cbz-protected dipeptide **52** in 89% yield, identical in all respects with the material from which the trifluoroacetamidooxazole was originally formed. In a similar fashion, the conversion of **46** back to dipeptide **45** was accomplished with $NaBH_4$ supported on neutral alumina in dry THF. These conditions were chosen so as to avoid the highly



51 52

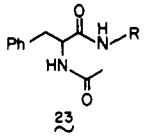
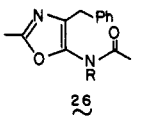
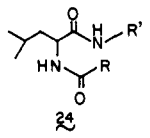
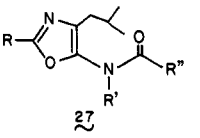
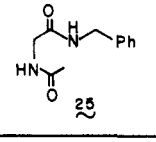
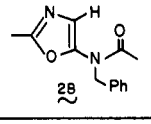
(26) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1982**, *22*, 1787.
(27) Anwir, M. K.; Spatola, A. F. *Synthesis*, **1980**, 929.
(28) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(29) Available from the Aldrich Chemical Company.
(30) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.
(31) Weygand, F.; Frauendorfer, E. *Chem. Ber.* **1970**, *103*, 2437.
(32) Herbst, R. M.; Shemin, D. "Organic Syntheses"; Wiley: New York, 1943; Collect Vol. II; p 11.
(33) Greenstein, J. P.; Winitz, M. "Chemistry of Amino Acids"; Wiley: New York, 1961; Vol. II.
(34) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1967**, *89*, 5012.
(35) The role of Super-Hydride in these reactions is actually as a base since, e.g., compound **54** has been prepared from **53** by using NaH in place



53 54

of $LiEt_3BH$ (see Experimental Section). This exchange process also works well with MeLi, and hence complete solubility of the anion is, perhaps, important. Apparently, therefore, N-acylation is likely to be occurring followed by hydrolysis of the imide to the amide during workup.

Table III. Preparation of 5-(Acylamino)oxazoles via Diamides

Entry	Diamide	Acid Halide (equiv)	Conditions	Product	Yield (%)
	 **23**			 **26**	
1	**23**, R = CH_2Ph	CH_3COCl (4)	$ZnBr_2$, CH_2Cl_2, Δ, 18h	**26**, R = CH_2Ph	73
		CH_3COBr (5)	$ZnBr_2$, $CHCl_3$, Δ, 5h		86
		CH_3COBr (3)	ZnI_2, $CHCl_3$, Δ, 5h		63
2	**23**, R = H	CH_3COBr (5)	$ZnBr_2$, $CHCl_3$, Δ, 3.5h	**26**, R = H	57
		CH_3COBr (2.5)	ZnI_2, $CHCl_3$, Δ, 5h		48
	 **24**			 **27**	
3	**24**, R = CH_3, R' = CH_2Ph	CH_3COBr (5)	$ZnBr_2$, $CHCl_3$, Δ, 4h	**27**, R = CH_3, R' = CH_2Ph, R" = CH_3	82
4	**24**, R = CH=CHPh, R' = $CH_2CH=CH_2$	 (5)	$ZnBr_2$, $CHCl_3$, Δ, 2h	**27**, R = CH=CHPh, R' = $CH_2CH=CH_2$, R" = p-$CH_3OC_6H_4$	44
5	**24**, R = CH_3, R' = H	PhCOCl (5)	ZnI_2, $CHCl_3$, Δ, 4h	**27**, R = CH_3, R' = H, R" = Ph	22
		PhCOCl (5)	$ZnBr_2$, $CHCl_3$, Δ, 4h	**27**, R = CH_3, R' = H, R" = Ph	20
		PhCOBr (2.5)	$ZnCl_2$, $CHCl_3$, Δ, 3.5h	**27**, R = CH_3, R' = H, R" = Ph	21
6	**24**, R = CH_3, R' = CH_2Ph	PhCOCl (2)	ZnI_2, $CHCl_3$, Δ, 4h	**27**, R = CH_3, R' = CH_2Ph, R" = Ph	35
		PhCOCl (5)	$ZnCl_2$, $CHCl_3$, Δ, 3h	**27**, R = CH_3, R' = CH_2Ph, R" = Ph	48
		PhCOBr (2.2)	$ZnCl_2$, $CHCl_3$, Δ, 7h	**27**, R = CH_3, R' = CH_2Ph, R" = Ph	47
7	 **25**	CH_3COBr (5)	$ZnBr_2$, $CHCl_3$, Δ, 4h	 **28**	59

basic medium characteristic of soluble BH_4^-. The stereochemical outcome at the originally racemic center in **45** via this cycle (**45** → **46** → **47** → **45**) is presently under investigation.

Summary

Both α-(acylamino)nitriles and diamides/dipeptides have been converted to 2,4-disubstituted 5-(acylamino)oxazoles upon exposure to an acid halide, the latter material affording either secondary or teritary amides. A variety of appendages on oxazole precursors can be tolerated during the cyclization step. Both carbon and nitrogen alkylation chemistry have been demonstrated as a potentially effective means of arriving at the target oxazolophanes. An entry into the optically active series, likewise, proceeds in a straightforward manner by using readily available chiral amino acids. Following manipulation of these heteroaromatic units (e.g., alkylation, deacylation), preliminary studies indicate that they undergo a facile and very efficient hydrolysis to form dipeptides. Thus, it has been shown that construction and handling of peptides need not only be thought of in a traditional sense, i.e., coupling via an activated carboxyl group with a primary or secondary amine. Appropriately functionalized oxazoles can now be considered synthetic equivalents of these important building blocks which naturally have completely different physical properties relative to polypeptides. The potential value of this concept, in this case within the context to a total synthesis of the (optically pure) cyclopeptide alkaloids, is under active investigation and will be reported in due course.

Experimental Section

Preparation of Diamides via Azlactones. A typical procedure is given for *N*-acetylphenylalanine *N*-benzylamide. Phenylalanine (5 g, 30 mmol) was added portionwise to hot (100 °C) acetic anhydride (50 mL) and stirred until homogeneous (ca. 10 min). Upon cooling to room temperature, excess Ac_2O and AcOH were removed at reduced pressure and the remaining oil was azeotroped with toluene (2 × 5 mL) and used in the next step without further purification. A sample for spectrochemical analysis was obtained by bulb-to-bulb distillation (Kugelrohr oven temperature 115 °C, 0.75 mmHg): ^1H NMR δ 2.1 (3 H, d, J = 2 Hz), 3.2 (2 H, m), 4.4 (1 H, m), 7.3 (5 H, br s); IR (neat, cm^{-1}) 1840, 1685; mass spectrum, m/e (relative intensity) 189 (65, M^+), 148 (14), 117 (23), 91 (100), 65 (57), 43 (100). 2-Methyl-4-benzyl-5-oxazolone (1.2 g, 6.2 mmol) in toluene (25 mL) was added to benzylamine (1 g, 10 mmol) in 25 mL of toluene at 80 °C over 30 min. After addition was complete, stirring was continued for 30 min, whereupon the heterogeneous reaction mixture was cooled, filtered, and washed with pentane to yield pure diamide: 1.4 g (77%), mp 163–164.5 °C (EtOAc/cyclohexane), R_f (EtOAc) 0.33: ^1H NMR δ 1.8 (3 H, s), 2.9 (2 H, d, J = 7 Hz), 4.2 (2 H, dd, J = 4, 1 Hz), 4.6 (1 H, apparent q, J = 7.8 Hz), 6.5 (1 H, d br, $J \sim 7$ Hz), 7.1 (6 H, br m); IR (CH_2Cl_2, cm^{-1}) 3420, 3300, 1658, 1500; mass spectrum, m/e (relative intensity) 296 (33, M^+), 237 (84), 163 (89), 162 (48), 120 (100), 106 (22), 91 (100), 65 (25), 43 (74).

***N*-Acetylphenylalanine amide**: mp 158–160 °C (95% EtOH/H_2O); R_f (9% EtOH/$CHCl_3$) 0.67; ^1H NMR (Me_2SO-d_6), δ 1.8 (3 H, s), 2.8 (2 H, m), 4.4 (1 H, m), 7.0 (1 H, s), 7.2 (5 H, s), 7.4 (1 H, s), 8.0 (1 H, d, J = 8 Hz); IR (KBr) cm^{-1} 3200, 1650–1600; mass spectrum, m/e (relative intensity) 206 (3, M^+), 162 (25), 147 (62), 91 (39), 73 (62), 43 (52).

***N*-Acetylleucine *N*-benzylamide**: mp 132–133 °C (EtOAc/cyclohexane); R_f (EtOAc) 0.40; IR (CH_2Cl_2) cm^{-1} 3425, 3300, 1660, 1520; ^1H NMR δ 0.90 (6 H, d, J = 6 Hz), 1.6 (3 H, br m), 1.9 (3 H, s), 4.3 (2 H, d, J = 6 Hz), 4.8 (1 H, br m), 6.3 (1 H, br d, J_{app} = 8 Hz), 6.9 (1 H, br s), 7.25 (5 H, s); mass spectrum, m/e (relative intensity) 262 (3, M^+), 206 (5), 129 (23), 128 (33), 91 (26), 86 (100), 43 (29).

***N*-Acetylleucine amide**: mp 204–206 °C (95% EtOH); R_f (10% MeOH/Et_2O) 0.28; ^1H NMR (Me_2SO-d_6) δ 0.77 (3 H, d, J = 4 Hz), 0.87 (3 H, d, J = 4 Hz), 1.4 (2 H, d, J = 7 Hz), 1.4 (1 H, br m), 1.8 (3 H), 4.15 (1 H, apparent q, J = 7 Hz), 6.85 (1 H, br s), 7.25 (1 H, br s) 7.8 (1 H, d, J = 10 Hz); IR (KBr) cm^{-1} 3200, 1640–1600; mass spectrum, m/e (relative intensity) 128 (70), 86 (100), 44 (70), 43 (91).

***N*-Acetylleucine *N*,*N*-dibenzylamide**: mp 104–106 °C (cyclohexane/EtOAc); R_f (Et_2O) 0.28; ^1H NMR δ 0.80 (6 H, t, J_{app} = 5 Hz),

1.5 (3 H, m), 1.9 (3 H, s), 4.5 (2 H, s), 4.5 (2 H, dd, J = 15 Hz), 5.1 (1 H, m), 6.8 (1 H, d, J = 9 Hz), 7.24 (10 H, m); IR (KBr, cm^{-1}) 3278, 1660, 1632; mass spectrum, m/e (relative intensity) 352 (1.1, M^+), 196 (39), 128 (52), 106 (91.9), 91 (100), 86 (100), 65 (29), 42 (46).

N-Acetylglycine N-benzylamide. Acetylglycine[32] (600 mg, 5.1 mmol) and triethylamine (0.71 mL, 5.1 mmol) were suspended in THF (7.5 mL) and cooled to −5 °C. Methyl chloroformate (0.40 mL, 5.1 mmol) was added dropwise and the mixture was stirred at this temperature for 30 min. Benzylamine (0.56 mL, 5.1 mmol) in THF (2.5 mL) was then added dropwise and stirring continued at −5 °C for 15 min and then at room temperature for 45 min. The reaction was then diluted with CH_2Cl_2 (50 mL) and poured into H_2O (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined extracts dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization (EtOAc) provided the title compound as a white amorphous solid: mp 141–143 °C; R_f (10% MeOH/CH_2Cl_2) 0.42; IR (KBr, cm^{-1}) 3310, 3245, 3200, 1645, 1532; ^1H NMR (Me_2SO-d_6) δ 1.86 (3 H, s), 3.71 (2 H, d, J = 7 Hz), 4.2 (2 H, d, J = 6 Hz), 7.2 (5 H, s); mass spectrum, m/e (relative intensity) 206 (7, M^+), 106 (97), 91 (84), 73 (64), 43 (40).

Preparation of N-cinnamoylleucine N-allylamide. Cinnamoyl chloride was coupled with DL-leucine methyl ester hydrochloride via standard procedures.[33] N-Cinnamoylleucine methyl ester (527 mg, 1.9 mmol) was dissolved in dioxane (2 mL) followed by dropwise addition of aqueous NaOH (0.5 mL, 4 M) and stirred for 3 h. The solution was then diluted with EtOAc (15 mL) and washed with H_2O (2 × 5 mL). The water extracts were cooled to 0 °C and acidified with aqueous HCl (2.1 mL, 1 N). Extraction with EtOAc (3 × 25 mL), drying over $MgSO_4$, and concentration in vacuo provided pure acid as a white semisolid, ~100%: R_f (EtOAc) 0.12; IR (KBr) cm^{-1} 3325, 3300, 1700, 1650; ^1H NMR (Me_2SO-d_6) δ 0.87 (6 H, d, J = 6 Hz), 1.5 (3 H, br m), 4.4 (1 H, m), 6.6 (1 H, d, J = 14 Hz), 7.3 (6 H, m), 8.2 (1 H, d, J = 9 Hz); mass spectrum, m/e (relative intensity) 217 (5), 205 (23), 131 (100), 103 (42), 69 (28). N-Cinnamoylleucine (536 mg, 1.7 mmol) was suspended in CH_2Cl_2 (1.7 mL) followed by addition of triethylamine (0.26 mL, 1.9 mmol), allylamine (0.14 mL, 1.8 mmol), and dicyclohexylcarbodiimide (380 mg, 1.8 mmol) in THF (1 mL). The mixture was stirred for 6 h at room temperature after which it was filtered and the filtrate diluted with $CHCl_3$ (25 mL) and washed with 1 N HCl, H_2O, 10% $NaHCO_3$, H_2O, and brine followed by drying over $MgSO_4$. Column chromatography on SiO_2 (20% EtOAc/CH_2Cl_2) followed by recrystallization (EtOAc) provided 450 mg (88%) of a white solid, mp 158–159 °C: R_f (EtOAc) 0.62; IR (CH_2Cl_2) cm^{-1} 3420, 3290, 1658, 1620; ^1H NMR δ 0.95 (6 H, d, J = 6 Hz), 1.6 (3 H, m), 3.8 (2 H, m), 4.6 (1 H, m), 5.1 (2 H, m), 5.8 (1 H, m), 6.2 (1 H, d, J = 15 Hz), 7.3 (5 H, m); mass spectrum, m/e (relative intensity) 244 (3), 216 (29), 131 (100), 103 (17), 77 (10); calcd for $C_{14}H_{18}NO$, 216.1389; found, 216.1394.

Carbobenzyloxyglycylphenylalanine N-benzylamide. Carbobenzyloxyglycylphenylalanine (175 mg, 0.5 mmol) was stirred in THF (1 mL) while triethylamine (69 μL, 0.5 mmol) was added and the solution was then cooled to −5 °C. Methyl chloroformate (38 μL, 0.5 mmol) was added dropwise and the heterogeneous mixture stirred for 30 min. Benzylamine (65 μL, 0.6 mmol) in THF (0.2 mL) was added and the reaction mixture was stirred at this temperature for 10 min followed by warming to room temperature for 40 min. The contents of the flask were poured into H_2O (10 mL), extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts washed with brine and dried over anhydrous Na_2SO_4. After concentrating in vacuo, recrystallization from EtOH/H_2O afforded 177 mg (80%), mp 136–137 °C: IR (KBr) cm^{-1} 3300, 3385, 1625, 1650, 1550; ^1H NMR δ 3.07 (2 H, m), 3.81 (2 H, d, J = 5.7 Hz), 4.3 (2 H, d, J = 5.7 Hz), 4.6 (1 H, m), 5.0 (2 H, s), 5.4 (1 H, br s), 6.3 (1 H, br s), 6.7 (1 H, d, J = 3.9 Hz), 7.2 (15 H, br m); mass spectrum, m/e (relative intensity), 237 (20), 120 (37), 106 (39), 91 (100); calcd for $C_{19}H_{19}N_3O_3$, 337.1426; found, 337.1417.

Typical Procedure for Ring Closure of Diamides with Trifluoroacetic Anhydride. 2-Methyl-4-isobutyl-5-(N-benzyltrifluoroacetamido)oxazole (9). In a 5-mL round-bottom flask was placed N-acetylleucine N-benzylamide (187 mg, 0.72 mmol), CH_2Cl_2 (0.7 mL), trifluoroacetic acid (0.5 mL), and trifluoroacetic anhydride (0.25 mL, 1.80 mmol). The reaction mixture was stirred at room temperature for 18 h, diluted with CCl_4 (2 mL), and concentrated via rotary evaporation. The oil was diluted with CH_2Cl_2 (10 mL) and added dropwise to ice cold saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the extracts combined, washed with brine, and dried ($MgSO_4$). Gravity column chromatography (25/1, $CHCl_3$/EtOAc) provided 220 mg (92%) of a colorless oil: R_f (25/1 $CHCl_3$/EtOAc) 0.42; IR (neat, cm^{-1}) 1722, 1660, 1580, 1210, 1165; ^1H NMR δ 0.77 (6 H, d, J = 7 Hz), 1.86 (3 H, m), 2.26 (3 H, s), 4.70 (2 H, s), 7.2 (5 H, s); mass spectrum, m/e (relative intensity) 340 (8, M^+), 231 (13), 119 (11), 91 (100), 43 (15); calcd for $C_{17}H_{19}N_2O_2F_3$, 340.1399; found, 340.1415.

2-Methyl-4-benzyl-5-(trifluoroacetamido)oxazole: 85%; mp 139–140 °C; R_f (Et_2O) 0.38; IR ($CHCl_3$, cm^{-1}) 3399, 3180, 1750, 1662, 1578, 1268, 1160; ^1H NMR δ 2.4 (3 H, s), 3.75 (2 H, s), 7.25 (6 H, br s); mass spectrum, m/e (relative intensity) 284 (55, M^+), 130 (63), 91 (52), 69 (24), 43 (100); calcd for $C_{13}H_{11}N_2O_2F_3$, 284.0773; found, 284.0782. Sample for combustion analysis recrystallized from Et_2O. Anal. Calcd for C, 54.92; H, 3.90; N, 9.86. Found C, 55.12; H, 3.76; N, 9.91.

2-Methyl-4-benzyl-5(N-benzyltrifluoroacetamido)oxazole: 82%; mp 83–84 °C; R_f (20% EtOAc/hexane) 0.23; IR ($CHCl_3$, cm^{-1}) 1720, 1655, 1572, 1235, 1160; ^1H NMR δ 2.35 (3 H, s), 3.4 (2 H, s), 4.63 (2 H, s), 7.1 (10 H, m); mass spectrum, m/e (relative intensity) 374 (15.6, M^+), 283 (6.1), 91 (100), 43 (100); calcd for $C_{20}H_{17}N_2O_2F_3$, 374.1241; found, 374.1207. Sample for combustion analysis recrystallized from Et_2O. Anal. Calcd for C, 64.15; H, 4.58; N, 7.49. Found: C, 64.37; H, 4.62; N, 7.43.

2-Methyl-4-benzyl-5-(N-allyltrifluoroacetamido)oxazole: 98%, oil; R_f (30% EtOAc/hexane) 0.49; IR (neat, cm^{-1}), 1730, 1660, 1575, 1220, 1165; ^1H NMR δ 2.4 (3 H, s), 3.7 (2 H, s), 4.0 (2 H, d, J = 9 Hz), 5.2 (2 H, m) 9.6 (1 H, m), 7.3 (5 H, m); mass spectrum, m/e (relative intensity) 324 (57, M^+), 283 (100), 119 (59), 91 (54), 43 (46); calcd for $C_{16}H_{15}N_2O_2F_3$, 324.1086; found 324.1090.

2-Methyl-5-(N-benzyltrifluoroacetamido)oxazole (11): 60%; oil; R_f (3/1, Skelly solve/Et_2O, 2 elutions) 0.37; IR (neat, cm^{-1}) 3125, 1770, 1621, 1265, 1160; ^1H NMR δ 2.3 (3 H, s), 4.7 (2 H, s), 6.4 (1 H, s), 7.2 (5 H, s); mass spectrum, m/e (relative intensity) 284 (5, M^+), 91 (100), 65 (9.4), 43 (9); calcd for $C_{13}H_{11}N_2O_2F_3$, 284.0772; found, 284.0793.

2-Methyl-4-isobutyl-5-(dibenzylamino)oxazole (10): 86%; oil; (chromatographed with 1% EtOAc/CH_2Cl_2 with 0.1% triethylamine), R_f (Et_2O) 0.80; IR (neat, cm^{-1}) 1665, 1678; ^1H NMR δ 0.8 (6 H, d, J = 6.6 Hz), 1.8 (1 H, septet J = 6.6 Hz), 1.9 (2 H, d, J = 7.2), 2.3 (3 H, s), 4.0 (4 H, s), 7.3 (10 H, m); mass spectrum, m/e (relative intensity) 334 (16, M^+), 291 (16), 91 (100), 43 (29); calcd for $C_{22}H_{26}N_2O$, 334.2044; found, 334.2040.

2-((Carbobenzyloxyamino)methyl)-4-benzyl-5-(N-benzyltrifluoroacetamido)oxazole (51). To the dipeptide **52** (40.3 mg, 0.0910 mmol) in CH_2Cl_2 (0.5 mL) was added trifluoroacetic acid (10 μL, 0.01 mmol) and trifluoroacetic anhydride (80 μL, 0.54 mmol). The mixture was stirred for 8 h at room temperature and following the usual workup procedures 43.8 mg (92%) of product was isolated as an oil after column chromatography (24/1, CH_2Cl_2/EtOAc): R_f (20/1, CH_2Cl_2/EtOAc) 0.26; IR (neat, cm^{-1}) 3320, 1720, 1655, 1240, 1220, 1160; ^1H NMR δ 3.4 (2 H, s), 4.3 (2 H, d, J = 6 Hz), 5.1 (2 H, s), 5.2 (1 H, br s), 7.2 (15 H, br, m); mass spectrum, m/e (relative intensity) 523 (1 , M^+), 415 (2), 108 (4), 91 (100), 65 (7), 43 (2); calcd for $C_{28}H_{24}N_3O_4F_3$, 523.1719; found, 523.1747.

General Procedure for Preparation of α-(Acylamino)nitriles. α-Isobutyl-α-(acetylamino)acetonitrile (12). To 1.79 g (12 mmol) of α-isobutyl-α-aminoacetonitrile hydrochloride in 40 mL of dichloromethane was added triethylamine (3.5 mL, 25 mmol). The mixture was cooled to −78 °C and acetyl chloride (1.16 mL, 13 mmol) in 10 mL of dichloromethane was added through an addition funnel over 30 min. The mixture was warmed to room temperature and stirred for 5 h. An equal volume of Et_2O was added and the mixture filtered to remove triethylamine hydrochloride. The mother liquor was concentrated in vacuo and purified by column chromatography on silica gel to give 1.81 g (97%) of a white solid: mp 48–49 °C; R_f (30% EtOAc/CH_2Cl_2) 0.49; IR (CH_2Cl_2, cm^{-1}) 3430, 3310, 2240, 1670; ^1H NMR δ 0.97 (6 H, d, J = 5.7 Hz), 1.62–1.93 (3 H, m), 4.88 (1 H, overlapping triplets), 6.55 (1 H, unresolved doublet); mass spectrum, m/e (relative intensity) 154 (1.0, M^+), 111 (48), 98 (94), 56 (62.5), 43 (100).

α-Benzyl-α-(cinnamoylamino)acetonitrile: 91%; mp 132–134 °C; R_f (30% EtOAc/CH_2Cl_2) 0.76; IR (CH_2Cl_2, cm^{-1}) 3420, 3300, 2240, 1675; ^1H NMR δ 3.13 (2 H, d, J = 6.8 Hz), 5.30 (1 H, m), 6.17 (1 H, unresolved doublet), 6.17 (1 H, d, J = 15.7 Hz), 7.33–7.52 (10 H, m), 7.67 (1 H, d, J = 15.7 Hz); mass spectrum, m/e (relative intensity) 276 (6.2, M^+), 147 (51.0), 146 (65), 131 (100), 103 (55.5), 91 (43), 77 (32).

α-Benzyl-α-(acetylamino)acetonitrile: 94%; mp 95–97 °C; R_f (30% EtOAc/CH_2Cl_2) 0.49; IR (CH_2Cl_2, cm^{-1}) 3420, 3320, 2240, 1685; ^1H NMR δ 1.95 (3 H, s), 3.06 (2 H, d, J = 6.9 Hz), 5.07 (1 H, overlapping triplets), 7.19 (1 H, br d), 7.30 (5 H, s); mass spectrum, m/e (relative intensity) 188 (26, M^+), 129 (100), 65 (31), 43 (90).

α-Benzyl-α-(benzoylamino)acetonitrile (14): 85%; mp 149–150 °C; R_f (30% EtOAc/CH_2Cl_2) 0.76; IR (CH_2Cl_2, cm^{-1}) 3420, 1675, 1600; ^1H NMR δ 3.19 (2 H, d, J = 6.5 Hz), 5.35 (1 H, overlapping triplets), 6.58 (1 H, br d), 7.34–7.77 (10 H, m); mass spectrum, m/e (relative intensity) 250 (21.1, M^+), 129 (70), 105 (100), 91 (76), 77 (59).

α-Isobutyl-α-((N-(carbomethoxy)glycyl)amino)acetonitrile (15): 47%; mp 70–71 °C; R_f (5% MeOH/Et_2O) 0.44; IR (CH_2Cl_2, cm^{-1}) 3410, 1730, 1690; ^1H NMR δ 0.90 (6 H, d, J = 6.4 Hz), 1.5–2.0 (3 H, m), 3.65 (3 H, s), 3.80 (2 H, d, J = 5.6 Hz), 4.6–4.9 (1 H, overlapping

triplets), 5.6 (1 H, br t), 7.0 (1 H, br d); mass spectrum, *m/e* (relative intensity) 228 (87), 201 (21.8), 171 (48).

α-Isobutyl-α-(formylamino)acetonitrile (16): 100%; R_f (Et_2O) 0.50; IR (neat, cm^{-1}) 2880, 2220, 1670; NMR δ 0.95 (6 H, d, J = 6 Hz), 1.51–1.21 (3 H, m), 4.6–4.9 (1 H, overlapping triplets), 7.8 (1 H, br d), 8.15 (1 H, s); mass spectrum, *m/e* (relative intensity) 97 (28), 84 (100), 57 (56), 41 (62), 29 (36).

α-Benzyl-α-((carbobenzyloxy)glycylamino)acetonitrile was prepared by the method of Anderson et al.[34] Thus, methyl chloroformate (0.40 mL, 5 mmol) was added to a solution of triethylamine (0.70 mL, 5 mmoles) in 10 mL of THF at 0 °C. After 1 min, Cbz-glycine (1.02 g, 4.9 mmoles) in 5 mL of THF was added; 2 min later, α-benzyl-α-aminoacetonitrile (0.75 g, 5.1 mmol) in 5 mL of THF was added and the mixture allowed to warm to room temperature and stir for 6 h. The mixture was quenched with 10 mL of 5% $NaHCO_3$ and diluted with 20 mL of EtOAc. Following extraction of the aqueous layer with EtOAc (3 × 15 mL), the combined extracts were washed with 24 mL of H_2O, dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography on silica gel to afford 880 mg (53%) of a white solid: mp 85–87 °C; R_f (Et_2O) 0.47; IR ($CHCl_3$, cm^{-1}) 3410, 3300, 1720, 1710, 1680; NMR δ 3.03 (2 H, d, J = 6.7 Hz), 3.79 (2 H, d, J = 5.9 Hz), 4.9–5.2 (1 H, m), 5.1 (2 H, s), 5.3 (1 H, br t), 6.9 (1 H, br d), 7.25–7.45 (10 H, m); mass spectrum, *m/e* (relative intensity) 130 (36.6), 129 (100), 91 (12).

α-(Cinnamylamino)acetonitrile: 89%; mp 104–105 °C; R_f (Et_2O) 0.33; IR (CH_2Cl_2, cm^{-1}) 1620; NMR (acetone-d_6) δ 4.30 (2 H, d, J = 6 Hz), 6.7 (1 H, d, J = 15 Hz), 7.1–7.8 (6 H, m), 7.9 (1 H, br s); mass spectrum, *m/e* (relative intensity) 186 (28, M^+), 131 (100), 103 (46), 86 (41).

General Procedure for Preparation of 5-(Acylamino)oxazoles from α-(Acylamino)acetonitriles. 2-Methyl-4-benzyl-5-acetamidooxazole. $BF_3{\cdot}Et_2O$ (0.67 mL, 5.3 mmol) and acetyl bromide (0.50 mL, 6.70 mmol) were dissolved in 20 mL of CH_2Cl_2 under an argon atmosphere. The solution was cooled to 0 °C and α-benzyl-α-(acetylamino)acetonitrile (1.0 g, 5.3 mmol) in 33 mL of CH_2Cl_2 was added through an addition funnel over 45 min. The resulting yellow solution was stirred for 4 h at 0 °C then quenched by slowly adding it to cold 5% $NaHCO_3$ (aq), followed by extraction of the aqueous layer several times with CH_2Cl_2, drying ($MgSO_4$), and concentration in vacuo. Chromatography on silica gel afforded 900 mg (73%) of a white solid: mp 131–133 °C; R_f (5% MeOH/Et_2O) 0.36; IR (CH_2Cl_2, cm^{-1}) 3400, 3360, 1710, 1665, 1605, 1580; NMR δ 1.81 and 1.97 (3 H, s), 2.33 and 2.38 (3 H, s), 3.75 (2 H, s), 6.98 (1 H, s), 7.26 (5 H, s); mass spectrum, *m/e* (relative intensity) 230 (61, M^+), 187 (48), 188 (100), 170 (35), 91 (63); calcd for $C_{13}H_{14}N_2O_2$, 230.1055; found, 230.1052.

2-(2-Phenylvinyl)-4-benzyl-5-acetamidooxazole: 100% mp 151–153 °C; R_f (Et_2O/pentane, 3/1) 0.25; IR (CH_2Cl_2, cm^{-1}) 3400, 3385, 1710, 1645; NMR δ 1.90 and 1.99 (3 H, s), 3.85 (2 H, s), 6.80 (1 H, d, J = 16.4 Hz), 6.96 (1 H, s), 7.33–7.55 (11 H, m); mass spectrum, *m/e* (relative intensity) 318 (15, M^+), 276 (95), 232 (40), 131 (90), 130 (50), 115 (42), 103 (65), 91 (100); calcd for $C_{20}H_{18}N_2O_2$, 318.1368; found, 318.1337.

2-(2-Phenylvinyl)-4-benzyl-5-((*p*-acetoxyphenyl)acetamido)oxazole, (19): 72%; mp 179–181 °C; R_f (Et_2O) 0.48; IR (CH_2Cl_2, cm^{-1}) 1760, 1710, 1645, 1200; NMR δ 2.26 (3 H, s), 3.50 (2 H, s), 3.78 (2 H, s), 6.70 (1 H, d, J = 16.4 Hz), 7.26–7.24 (16 H, m); mass spectrum, *m/e* (relative intensity) 452 (33, M^+), 276 (100), 231 (50), 131 (94), 107 (95), 91 (50), 43 (26); calcd for $C_{28}H_{24}N_2O_4$, 452.1735, found, 452.1733. Sample for combustion analysis recrystallized from CH_2Cl_2/Skelly Solve. Anal. Calcd for C, 74.31; H, 5.35; N, 6.19. Found: C, 74.15; H, 5.44; N, 6.00.

2-(((Carbomethoxy)amino)methyl)-4-isobutyl-5-acetamidooxazole (21): 72% R_f (5% MeOH/Et_2O) 0.36; IR (neat, cm^{-1}) 3280, 1730, 1710, 1690, 1660; NMR δ 0.88–0.92 (6 H, overlapping doublets), 1.9–2.0 (1 H, m), 1.92 and 2.15 (3 H, s), 2.23–2.28 (2 H, overlapping doublets), 3.70 (3 H, s), 4.40 (2 H, d, J = 5.8 Hz), 5.45 (1 H, br d), 7.21 (1 H, s); mass spectrum, *m/e* (relative intensity) 269 (13, M^+), 227 (60), 184 (44), 88 (88), 43 (100); calcd for $C_{12}H_{18}N_3O_4$, 269.1375; found, 269.1374.

2-Methyl-4-isobutyl-5-acetamidooxazole: 70%; R_f (Et_2O) 0.23; IR (neat, cm^{-1}) 3400, 1690, 1660; NMR δ 0.89–0.92 (6 H, overlapping doublets), 1.93 and 2.15 (3 H, s), 1.90–2.10 (1 H, m), 2.22–2.27 (2 H, overlapping doublets), 2.37 and 2.40 (3 H, s), 7.28 and 7.44 (1 H, s); mass spectrum, *m/e* (relative intensity) 196 (8, M^+), 154 (39), 111 (100), 83 (40), 43 (40); calcd for $C_{10}H_{16}N_2O_2$, 196.1211; found, 196.1246.

2-Methyl-4-isobutyl-5-(dichloroacetamido)oxazole: 46%; mp 85–88° C; R_f (Et_2O) 0.49; IR (CH_2Cl_2, cm^{-1}) 1735, 1665, 1575; NMR δ 0.90 (6 H, d, J = 6.4 Hz), 1.8–2.1 (1 H, m), 2.26 (2 H, d, J = 6.2 Hz), 2.40 (3 H, s), 6.04 (1 H, s), 8.18 (1 H, s); mass spectrum, *m/e* (relative intensity) 266 (31), 264 (41), 233 (47), 221 (100), 195 (75), 131 (43), 43 (68); calcd for $C_{10}H_{14}N_2O_2Cl_2$, 268.0352; found, 268.0382.

2-Phenyl-4-benzyl-5-acetamidooxazole (20): 63%; mp 157–159 °C; R_f (3/1, Et_2O/pentane) 0.28; IR (CH_2Cl_2, cm^{-1}) 1715, 1655, 1605; NMR δ 1.85 and 2.0 (3 H, s), 3.89 and 3.91 (2 H, s), 6.85 and 7.0 (1 H, s), 7.20–8.15 (10 H, m); mass spectrum, *m/e* (relative intensity) 292 (59, M^+), 250 (100), 77 (100), 43 (88); calcd for $C_{18}H_{16}N_2O_2$, 292.1211; found, 292.1211.

2-(((Carbobenzyloxy)amino)methyl)-4-benzyl-5-acetamidooxazole (21): 69%; mp 104–105 °C; R_f (Et_2O) 0.25; IR (CH_2Cl_2, cm^{-1}) 3440, 3405, 3290, 1720, 1705, 1690, 1660, 1220; NMR δ 1.64 and 1.98 (3 H, s), 3.77 (2 H, s), 4.38 (2 H, d, J = 5.7 Hz), 5.12 (2 H, s), 5.35 (1 H, br s), 6.70 (1 H, br s), 7.25–7.40 (10 H, m); mass spectrum, *m/e* (relative intensity), 379 (1, M^+), 337 (42), 229 (55), 91 (100); calcd for $C_{21}H_{21}N_3O_4$, 379.1531; found, 379.1522.

4-Isobutyl-5-(trimethylacetamido)oxazole (22): 74%; oil; R_f (Et_2O) 0.43; IR (CH_2Cl_2, cm^{-1}) 3420, 1700, 1655, 1570; NMR δ 0.89 (6 H, d, J = 6.6 Hz), 1.30 (9 H, s), 2.00 (1 H, m), 2.27 (2 H, d, J = 6.9 Hz), 6.98 (1 H, br s), 7.68 (1 H, s); mass spectrum, *m/e* (relative intensity) 224 (5, M^+), 97 (24), 85 (16), 57 (100); calcd for $C_{12}H_{20}N_2O_2$, 224.1522; found, 224.1513.

Typical Procedure for Preparation of 5-(acylamino)oxazoles from Diamides. 2-Methyl-4-isobutyl-5-(*N*-benzylacetamido)oxazole. A 10-mL round-bottom flask was charged with $ZnBr_2$ (260 mg, 1.2 mmol), $CHCl_3$ (0.6 mL), and *N*-acetylleucine-*N*-benzylamide (150 mg, 0.6 mmol). A reflux condenser was attached followed by addition of acetyl bromide (0.21 mL, 3 mmol). The heterogeneous mixture was gently refluxed for 4.5 h. The two-phase reaction mixture was allowed to cool, diluted with 5 mL of dry THF and stirred until homogeneous (~5 min), followed by dropwise addition to 20 mL of ice-cold saturated $NaHCO_3$. The mixture was filtered through a small pad of Celite and washed liberally with CH_2Cl_2 (3 × 30 mL) and the organic extracts were separated and dried (Na_2SO_4). Flash chromatography (40% EtOAc/petroleum ether) gave 132 mg (80%) of a pale yellow oil: R_f (60% EtOAc/$CHCl_3$) 0.52; IR (neat, cm^{-1}) 1691, 1660; NMR δ 0.76 (6 H, d, J = 7 Hz), 1.2 (1 H, m), 1.9 (5 H, br s), 2.2 (3 H, s), 4.3 (2 H, s), 7.1 (5 H, s); mass spectrum, *m/e* (relative intensity) 286 (13, M^+), 244 (35), 201 (41), 91 (100), 69 (86), 43 (25); calcd for $C_{17}H_{22}N_2O_2$, 286.1680; found, 286.1687.

2-Methyl-4-isobutyl-5-benzamidooxazole: 20%; pale yellow oil; R_f (Et_2O) 0.38; IR (neat, cm^{-1}) 3260, 1665, 1565; NMR δ 0.86 (6 H, d, J = 10 Hz), 2.1 (3 H, br m); 2.4 (3 H, s), 7.6 (6 H, br m); mass spectrum, *m/e* (relative intensity) 258 (5, M^+), 121 (7), 106 (9), 105 (100), 77 (31), 43 (10); calcd for $C_{15}H_{18}N_2O_2$, 258.1367; found, 258.1377.

2-Methyl-5-(*N*-benzylacetamido)oxazole (28): 59%; yellow oil; R_f (Et_2O) 0.32; IR (CH_2Cl_2, cm^{-1}) 3122, 1710, 1662, 1570; ^1H NMR δ 1.8 and 1.9 (3 H, s), 2.3 and 2.4 (3 H, s), 4.7 (2 H, s), 6.4 and 6.75 (1 H, s), 7.5 (5 H, s); mass spectrum, *m/e* (relative intensity) 230 (2, M^+), 188 (42), 98 (20), 91 (100), 43 (34); calcd for $C_{13}H_{14}N_2O_2$, 230.1056; found, 230.1040.

2-Methyl-4-benzyl-5-acetamidooxazole: 57%; physical as well as spectroscopic data identical with that of a sample prepared via the corresponding amide nitrile (vide supra).

2-Methyl-4-benzyl-5-(*N*-benzylacetamido)oxazole: 86%; oil; R_f (EtOAc) 0.63; IR (neat, cm^{-1}) 1690, 1659, 1572; ^1H NMR δ 1.95 (3 H, s), 2.3 (3 H, s), 3.25 (2 H, s), 4.6 (2 H, s), 7.0 (10 H, m); mass spectrum, *m/e* (relative intensity) 320 (13, M^+), 278 (100), 229 (31), 187 (47), 91 (100), 43 (100); calcd for $C_{20}H_{20}N_2O_2$, 320.1523; found, 320.1534.

2-Methyl-4-isobutyl-5-(*N*-benzylbenzamido)oxazole: 48%; oil; R_f (EtOAc) 0.30; IR (neat, cm^{-1}) 1660, 1580; ^1H NMR δ 0.52 (6 H, d, J = 9 Hz), 1.5 (3 H, br s), 2.3 (3 H, s), 4.9 (2 H, s), 7.3 (10 H, br s); mass spectrum, *m/e* (relative intensity) 348 (16, M^+), 105 (100), 91 (31), 77 (23), 43 (16), 28 (12); calcd for $C_{22}H_{24}N_2O_2$, 348.1836; found, 348.1826.

2-(2-Phenylvinyl)-4-isobutyl-5-(*N*-allylanisamido)oxazole: 44%; oil; R_f (CH_2Cl_2) 0.22; IR (neat, cm^{-1}) 1662, 1645, 1610, 1515; ^1H NMR δ 0.70 (6 H, d, J = 6 Hz), 3.8 (3 H, s), 4.4 (2 H, d, J = 6 Hz), 5.2 (2 H, m), 6.01 (1 H, m), 6.7 (2 H, m), 6.8 (1 H, d of dd, J = 18 Hz), 7.4 (9 H, m); mass spectrum, *m/e* (relative intensity) 416 (31, M^+), 135 (100), 131 (50), 41 (16): calcd for $C_{26}H_{28}N_2O_3$, 416.2098; found, 416.2120.

General Procedure for N-Alkylation of 5-Acetamidooxazoles. 2-Methyl-4-benzyl-5-[*N*-(((*p*-benzyloxyphenyl)carbonyl)methyl)acetamido]oxazole. 2-Methyl-4-benzyl-5-acetamidooxazole (88 mg, 0.38 mmol) was dissolved in 2 mL of THF and cooled to 0 °C. NaH (20 mg, 0.41 mmol, 50% oil dispersion) was added at once under a stream of argon producing a light yellow solution. *n*-Bu_4NCl (100 mg, 0.38 mmol) was next added and the mixture stirred for 15 min prior to addition of *p*-benzyloxy-α-bromoacetophenone (123 mg, 0.40 mmol). The mixture was warmed to room temperature and stirred for 1 h and then quenched carefully with H_2O and transferred into a separatory funnel. Several extractions with Et_2O (3 × 5 mL) were followed by drying ($MgSO_4$) the extracts and concentration in vacuo. Chromatography on silica gel 60

(Merck) afforded 131 mg (82%) of a white solid: mp 111–114 °C; R_f (Et_2O) 0.33; IR (CH_2Cl_2, cm^{-1}) 1690, 1660, 1600; NMR δ 1.89 (3 H, s), 2.38 (3 H, s), 4.78 (2 H, s), 5.10 (2 H, s), 6.92–7.91 (14 H, m); mass spectrum, *m/e* (relative intensity) 454 (10, M^+), 413 (51), 229 (53), 201 (100), 91 (87), 43 (18); calcd for $C_{28}H_{26}N_2O_4$, 454.1915, found, 454.1908. A sample for combustion analyses was recrystallized from Et_2O. Anal. Calcd for C, 73.97; H, 5.76; N, 6.17. Found: C, 73.82; H, 5.88; N, 6.13.

2-Methyl-4-benzyl-5-(*N*-(2-bromopropenyl)acetamido)oxazole: 77%; R_f (Et_2O) 0.41; IR (neat, cm^{-1}) 1695, 1660, 1640; NMR δ 1.84 (3 H, s), 2.41 (3 H, s), 3.78 (2 H, s), 4.33 (2 H, s), 5.52 (1 H, d, J = 2 Hz), 5.69 (1 H, d, J = 2 Hz), 7.29 (5 H, s); mass spectrum, *m/e* (relative intensity) 350 (5.6), 348 (6.4), 308 (26.5), 306 (25.5), 186 (19), 91 (20), 43 (100); calcd for $C_{16}H_{17}N_2O_2{}^{79}Br$, 348.0516; found, 348.0494.

2-Methyl-4-benzyl-5-(*N*-(*p*-benzyloxyphenyl)ethyl)acetamido)oxazole: 73%; R_f (1/1/0.1 pentane/Et_2O/MeOH) 0.35; IR (neat, cm^{-1}) 1690, 1660, 1610; NMR δ 1.78 (3 H, s), 2.37 (3 H, s), 2.64–2.84 (2 H, m), 3.68 (2 H, t, J = 8 Hz), 3.65 (2 H, s), 5.0 (2 H, s), 6.79–7.44 (14 H, m); mass spectrum, *m/e* (relative intensity) 440 (1.7, M^+), 230 (74), 188 (64), 91 (100), 43 (38); calcd for $C_{28}H_{28}N_2O_3$, 440.2085; found, 440.2092.

2-(2-Phenylvinyl)-5-[*N*-(((*p*-benzyloxyphenyl)carbonyl)methyl)acetamido]oxazole: 66%; R_f (Et_2O) 0.37; IR (neat, cm^{-1} 1690, 1640, 1605, 1230; NMR δ 2.1 (3 H, s), 5.0 (2 H, s), 5.1 (2 H, s), 6.8–8.0 (16 H, m); mass spectrum, *m/e* (relative intensity) 454 (1.1, M^+), 410 (20), 211 (36), 131 (9), 91 (100), 43 (11); calcd for $C_{26}H_{22}N_2O_3$ (M^+ – CH_3CHO), 410.1598; found, 410.1613.

***N*-Alkylation of 2-(((Carbobenzyloxy)amino)methyl)-5-(acylamino)-oxazoles via Dianion Chemistry.** The *N*-alkylation of these materials was performed under similar conditions described earlier except, 2.2 equiv of NaH and 2.0 equiv of nBu_4NCl were used. 2-(((Carbobenzyloxy)-amino)methyl)-4-benzyl-5-(benzylacetamido)oxazole (**42**): 76%; R_f (Et_2O) 0.50; IR (neat, cm^{-1}) 1690, 1655; ^1H NMR δ 1.68 and 1.78 (3 H, s), 3.35 (3 H, s), 4.39 (2 H, d, J = 5.7 Hz), 4.69 (2 H, s), 5.13 (2 H, s), 5.36 (1 H, br s), 6.96–7.45 (15 H, m); mass spectrum, *m/e* (relative intensity) 469 (4 M^+), 319 (51), 91 (100), 57 (26); calcd for $C_{28}H_{27}N_3O_4$, 469.2001; found, 469.2007.

2-(((Carbobenzyloxy)amino)methyl)-4-benzyl-5-[(*p*-(benzyloxy)-phenethyl)acetylamino]oxazole (43): 33%; R_f (Et_2O) 0.33; IR (CCl_4, cm^{-1}) 3300, 3040, 2940, 1730, 1705, 1665, 1625, 1240; ^1H NMR δ 1.98 and 1.75 (3 H, s), 2.80 (2 H, m), 3.52–3.81 (4 H, m), 4.39 (2 H, d, J = 6.0 Hz), 5.02 (2 H, s), 5.15 (2 H, s), 6.85–7.41 (20 H, m); mass spectrum, *m/e* (relative intensity) 279 (5), 213 (6), 167 (14), 149 (38), 118 (13), 91 (100); calcd for $C_{36}H_{36}N_3O_5$ (M^+ + 1), 590.2655; found, 590.2650 (chemical ionization).

Metalation and Condensation of Alkoxyoxazole 31 with Benzaldehyde. 2-Methyl-4-isobutyl-5-methoxyoxazole (97 mg, 0.58 mmol) was dissolved in THF (0.6 mL) and transferred via cannula to LDA (1.2 mmol, 1 M) at −78 °C. After 1 h at this temperature, benzaldehyde (64 μL, 0.63 mmol) was added neat and stirred for 5 min. The reaction was quenched with pH 7 buffer (1 mL) and the contents of the flask poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 25 mL), and dried over anhydrous K_2CO_3. Concentration in vacuo and column chromatography on Florisil provided 117 mg (74%) of a colorless oil: R_f (2/1, pentane/ether) 0.42; IR (neat, cm^{-1}) 3400, 1670, 1570; NMR δ 0.9 (6 H, d, J = 8 Hz), 1.9 (1 H, m), 2.2 (2 H, d, J = 6 Hz), 3.8 (3 H, s), 5.1 (1 H, t, J = 6 Hz), 7.3 (6 H, br s); mass spectrum, *m/e* (relative intensity) 275 (6, M^+), 274 (14), 257 (96), 214 (100), 131 (59), 105 (34), 43 (13); calcd for $C_{16}H_{21}NO_3$, 275.1521; found, 275,1523.

Typical Procedure for Metalation and Reaction of 2-Methyl-5-benzamidooxazoles with LDA. 2-(2-Hydroxy-3-methyl)butyl-4-benzyl-5-benzamidooxazole (38a). 2-Methyl-4-benzyl-5-benzamidooxazole (72 mg, 0.24 mmol) was dissolved in 0.40 mL THF, cooled to −78 °C, and was then slowly added via cannula to a 1 M solution of LDA (0.67 mmol) producing a deep red dianion. This mixture was stirred at −78 °C for 1 h followed by the introduction of isobutyraldehyde (65 μL, 0.79 mmol) dissolved in 0.5 mL of THF, at −78 °C, via cannula. After stirring at this temperature for 5 min, the mixture was carefully quenched with pH 7 buffer and allowed to warm to room temperature. Extraction of the aqueous layer with Et_2O (3 × 5 mL), drying ($MgSO_4$), and concentration in vacuo gave the crude material which was chromatographed on silica gel to afford 60 mg (69%) of a light yellow oil: R_f (20% EtOAc/CH_2Cl_2) 0.30; IR (CH_2Cl_2, cm^{-1}) 3500, 3410, 3080, 1695, 1600; ^1H NMR δ 0.95–1.00 (6 H, overlapping doublets), 1.78 (1 H, m), 2.70–2.91 (2 H, m), 3.80 (1 H, m), 3.85 (2 H, s), 7.15–7.76 (11 H, m); mass spectrum, *m/e* (relative intensity) 364 (5, M^+), 292 (26), 105 (100), 77 (26); calcd for $C_{22}H_{24}N_2O_3$, 364.1786; found, 364.1772.

2-(2-Phenylethyl)-4-benzyl-5-benzamidooxazole (38b): 79%; R_f (40% EtOAc/Skelly Solve) 0.43; IR (neat, cm^{-1}) 3380, 1690, 1660, 1600; ^1H NMR δ 3.01 (4 H, s), 3.84 (2 H, s), 7.21–7.61 (11 H, m); mass spectrum, *m/e* (relative intensity) 382 (21, M^+), 291 (12), 91 (100); calcd for $C_{25}H_{22}N_2O_2$, 382.1681; found, 382.1675.

Carbobenzyloxy-L-leucylphenylalanine *N*-Benzylamide (45). To carbobenzyloxy-L-leucine (234 mg, 0.939 mmd) in DMF (3 mL) were added at 0 °C 1-hydroxybenzotriazole (155 mg, 1.141 mmol), dicyclohexylcarbodiimide (208 mg, 1.007 mmol), and DL-phenylalanine-*N*-benzylamide (228 mg, 0.898 mmol). After 1 h, the reaction was brought to room temperature and stirred for an additional 20 h. It was then filtered and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (100 mL) and washed with 1 N HCl (15 mL), H_2O (15 mL), 10% $NaHCO_3$ (15 mL), H_2O (15 mL), and brine (15 mL) and dried over Na_2SO_4. Column chromatography (20% EtOAc/CH_2Cl_2) followed by recrystallization (95% EtOH) gave 174 mg (40%) of an amorphous powder as a mixture of diastereomers: mp 96–98 °C; R_f (20% EtOAc/Skelly Solve) 0.32; ^1H NMR consisted of complex multiplets, δ 0.89 (6 H, m), 1.40 (3 H, m), 3.06 (2 H, m), 4.03 (1 H, m), 4.29 (2 H, m), 5.00 (2 H, s), 7.20 (15 H, m); IR (KBr) cm^{-1} 3300, 1695, 1645, 1545, 1240; mass spectrum, *m/e* (relative intensity) 350 (7), 237 (20), 91 (97), 56 (100); calcd for $C_{16}H_{15}NO$, 237.1163; found, 237.1153.

2-[1(*S*)-(Carbobenzyloxyamino)-3-methylbutyl]-4-benzyl-5-(*N*-benzyltrifluoroacetamido)oxazole (46, R = CH_2Ph). Dipeptide **45** (127 mg, 0.254 mmol) was dissolved in $CHCl_3$ (0.5 mL) and cooled to 0 °C. Trifluoroacetic anhydride (0.11 mL, 0.762 mmol) and trifluoroacetic acid (15 μL, 0.172 mmol) were then added and the resulting solution was allowed to stand for 19 h with gradual warming to room temperature. Usual workup and chromatography (17% EtOAc/Skelly Solve) provided 145 mg (98%) of a colorless oil: R_f (20% EtOAc/Skelly Solve) 0.42; ^1H NMR δ 0.89 (6 H, d, J = 2.7 Hz), 1.55 (3 H, m), 3.51 (2 H, s), 4.54 (2 H, dd, J = 14.1 Hz), 4.92 (1 H, m), 5.11 (2 H, s), 7.01–7.47 (11 H, m); IR (CCl_4, cm^{-1}) 3420, 1730, 1700, 1660, 1570, 1225, 1165; mass spectrum, *m/e* (relative intensity) 579 (M^+, 3), 471 (2), 444 (1), 108 (3), 91 (100), 65 (3), 43 (3); calcd for $C_{32}H_{32}N_3O_3F_3$, 579.2344; found, 579.2320.

Ring Opening of Oxazole 46 to Dipeptide 45. Oxazole **46**, R = CH_2Ph (50 mg, 0.0860 mmol), was dissolved in THF (0.6 mL) and cooled to 0 °C. $NaBH_4$/Alumina (66 mg 0.069 mmol, 10% $NaBH_4$) was added in several portions under a stream of Argon and the heterogeneous mixture stirred for 75 min. It was then filtered through Celite and concentrated in vacuo. The residue was dissolved in 0.4 mL HOAc/THF/H_2O (3:1:1) and stirred at 0 °C for 1.75 h. Solvent was removed in vacuo and the residue was azeotroped with toluene (1.5 mL). The crude product was immediately chromatographed on silica gel eluting with 20% EtOAc/CH_2Cl_2 to give 36 mg (86%) of the dipeptide identical with an authetic sample.

Ring Opening of Oxazole 51, Compound **51** (26.0 mg, 0.0496 mmol) was dissolved in EtOH (0.2 mL) and cooled to −78 °C. $NaBH_4$ (1 mg, 0.1053 mmol) was added and the reaction stirred for 1.5 h at −78 °C and 15 min at −25 °C. The reaction was diluted with CH_2Cl_2 (5 mL), poured into cold pH 7 buffer and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with cold 10% $NaHCO_3$ and concentrated in vacuo to give a yellow oil. The oil was dissolved in THF/HOAc/H_2O (5:2:1) and stirred at 0 °C for 1 h and then at room temperature for 1 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 × 25 mL), and the extracts were washed with brine and dried over Na_2SO_4. Preparative TLC (50% EtOAc/petroleum ether) afforded 19.5 mg (89%) of the dipeptide, identical with an authentic sample (TLC, mmp, IR, NMR, mass spectroscopy).

2-Methyl-4-isobutyl-5-acetamidooxazole (49) via 2-Methyl-4-isobutyl-5-(trifluoroacetamido)oxazole 48b with Super-Hydride. Oxazole **48b** (37.0 mg, 0.148 mmol) was dissolved in THF (0.3 mL) and cooled to −78 °C. Super-Hydride (0.30 mL, 0.300 mmol, 1 M in THF) was added dropwise and stirring was continued for 30 min after which the solution was warmed to 0 °C and transferred via cannula to acetic anhydride (0.25 mL, 2.65 mmol) in THF (0.1 mL). Stirring was continued for 2 h with gradual warming to room temperature at which point it was poured into H_2O (5 mL) and extracted with $CHCl_3$ (2 × 5 mL). The organics were combined and washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Column chromatography (80% EtOAc/$CHCl_3$) provided 20 mg (69%) of the oxazole identical with that prepared via the corresponding amide nitrile.

2-Methyl-4-isobutyl-5-benzamidooxazole via 2-Methyl-4-isobutyl-5-(trifluoroacetamido)oxazole 48b with Super-Hydride. In a similar manner to that described above, oxazole **48b** (62.5 mg, 0.2500 mmol) gave benzamidooxazole **49b** (52 mg, 81%) identical with material prepared via the corresponding amide nitrile.

Following the above procedure, the following oxazole derivatives were prepared.

2-(((Carbobenzyloxy)amino)methyl)-4-benzyl-5-((carbomethoxy)-amino)oxazole (49a): 52% (94% based on recovered starting material; R_f (20% EtOAc/CH_2Cl_2) 0.45; IR ($CHCl_3$) cm^{-1} 3460, 3420, 1740,

1730, 1620, 1240; ^{1}H NMR δ 3.71 (3 H, s), 3.77 (2 H, s), 4.39 (2 H, d, J = 5.7 Hz), 5.12 (2 H, s), 5.18 (1 H, br s), 6.07 (1 H, br s), 7.28 (10 H, m); mass spectrum, m/e (relative intensity) 149 (39), 91 (65), 71 (35), 43 (100); calcd for $C_{21}H_{22}N_3O_5$ (chemical ionization, M + 1), 396.1559; found, 396.1604.

2-(2-Phenylvinyl)-4-isobutyl-5-((carbomethoxy)amino)oxazole (49c): 85%; mp 134–136 °C; R_f (1:1 Et_2O/Skelly solve); IR (CH_2Cl_2) cm^{-1} 3690, 3405, 3025, 2860, 1810, 1750, 1660; ^{1}H NMR δ 0.94 (6 H, d, J = 6.6 Hz), 2.05 (1 H, m), 2.30 (2 H, d, J = 7.2 Hz), 3.79 (3 H, s), 6.25 (1 H, br s), 6.83 (1 H, d, J = 16.5 Hz), 7.25–7.51 (5 H, m); mass spectrum, m/e (relative intensity) 300 (53, M$^+$), 268 (50), 225 (32), 197 (65), 129 (100), 103 (55); calcd for $C_{17}H_{20}N_2O_3$, 300.1448; found, 300.1461.

2-[1(S)-(Carbobenzyloxyamino)-3-methylbutyl]-4-benzyl-5-(trimethylacetamido)oxazole: 41%; R_f (20% EtOAc/Skelly Solve) 0.13; IR (CCl_4, cm^{-1}) 3440, 3310, 1730, 1710, 1660; NMR δ 0.94 (6 H, d, J = 6 Hz), 1.23 (9 H, s), 1.69 (3 H, s), 3.79 (2 H, s), 5.09 (2 H, s), 6.69 (1 H, br s), 7.23 (5 H, s), 7.28 (5 H, s); mass spectrum, m/e (relative intensity) 477 (7, M$^+$), 285 (12), 91 (97), 57 (100); calcd for $C_{28}H_{35}N_3O_4$, 477.2628; found, 477.2609.

2-Methyl-4-benzyl-5-acetamidooxazole (54) via 2-Methyl-4-benzyl-5-(trifluoroacetamido)oxazole with Sodium Hydride. To oxazole **53** (33.0 mg, 0.1162 mmol) in THF (0.3 mL) was added sodium hydride (12 mg, 0.2300 mmol 56% dispersion) at 0 °C. After hydrogen evolution was complete (~15 min) the reaction mixture was transferred via cannula to acetyl chloride (41 μL, 0.581 mmol) in THF (0.1 mL) at 0 °C. Washing with THF (2 × 75 μL) brought the substrate concentration to about 0.2 M. Stirring was continued for 2 h with gradual warming to room temperature at which point the reaction was quenched with saturated $NaHCO_3$ (1.5 mL) and stirred overnight. Following aqueous workup and column chromatography (80% EtOAc/CH_2Cl_2), 13.3 mg (50%) of a pale yellow solid was obtained, identical with a sample prepared via the corresponding amide nitrile.

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Registry No. (*S*)-**5** (R = CH_2Ph), 87783-58-2; (*S*)-**5** (R = $CH_2CH=CH_2$), 87783-59-3; (*S*)-**5** (R = H), 7376-90-1; (*S*)-**6** (R = H), 87783-60-6; (*S*)-**6** (R = CH_2Ph), 87783-61-7; **7**, 69753-67-9; **8** (R = CH_2Ph), 87783-62-8; **8** (R = $CH_2CH=CH_2$), 87783-63-9; **8** (R = H), 87784-06-3; **9**, 87783-64-0; **10**, 87783-65-1; **11**, 87783-66-2; **12** (R = $CH_2CH(CH_3)_2$), 87783-67-3; **12** (R = CH_2Ph), 24748-46-7; **13** (R = CH_2Ph), 87783-68-4; **13** (R = H), 87783-69-5; **14**, 87783-70-8; **15** (R = $CH_2CH(CH_3)_2$; R′ = CH_3), 87783-71-9; **15** (R = R′ = CH_2Ph), 87783-72-0; **16**, 27395-05-7; **17** (R = $CH_2CH(CH_3)_2$; R′ = $COCH_3$), 87783-73-1; **17** (R = $CH_2CH(CH_3)_2$; R′ = $COCHCl_2$), 87783-74-2; **17** (R = CH_2Ph; R′ = $COCH_3$), 87783-75-3; **18** (R = CH_2Ph), 87783-76-4; **18** (R = H), 87783-77-5; **19**, 87783-78-6; **20**, 87783-79-7; **21** (R = $CH_2CH(CH_3)_2$; R′ = CH_3), 87783-80-0; **21** (R = $CH_2CH(CH_3)_2$; R′ = CH_3), 87783-81-1; **21** (R = R′ = CH_2Ph), 87783-82-2; **22**, 87783-83-3; (*S*)-**24** (R = CH=CHPh; R′ = $CH_2CH=CH_2$), 87783-84-4; (*S*)-**24** (R = CH_3; R′ = H), 28529-34-2; **26** (R = CH_2Ph), 87783-85-5; **23** (R = CH_3; R′ = CH_2Ph; R″ = CH_3), 87783-86-6; **27** (R = CH=CHPh; R′ = $CH_2CH=CH_2$; R″ = p-$CH_3OC_6H_4$), 87783-87-7; **27** (R = CH_3; R′ = H; R″ = Ph), 87783-88-8; **27** (R = CH_3; R′ = CH_2Ph; R″ = Ph), 87783-89-9; **28**, 87783-90-2; **31**, 87783-91-3; **32**, 87783-92-4; **38a**, 87783-93-5; **40a**, 87783-94-6; **42**, 87783-95-7; **43**, 87783-96-8; (L,L)-**45**, 87783-97-9; (L,D)-**45**, 87783-98-0; (*S*)-**46**, 87783-99-1; **48b**, 87784-00-7; **49a**, 87784-01-8; **49c**, 87784-02-9; **50**, 87784-03-0; **51**, 87784-04-1; (L)-**52**, 87784-05-2; **53**, 87784-06-3; *t*-BuCOCl, 3282-30-2; CH_3COCl, 75-36-5; CH_3COBr, 506-96-7; p-$CH_3OC_6H_4COCl$, 100-07-2; PhCOCl, 98-88-4; PhCOBr, 618-32-6; $Cl_2CHCOCl$, 79-36-7; p-$AcOC_6H_4CH_2COCl$, 65448-20-6; TFAA, 407-25-0; 2-methyl-4-benzyl-5-[*N*-(((*p*-benzoxyphenyl)carbonyl)methyl)acetamido]oxazole, 87784-07-4; 2-methyl-4-benzyl-5-(*N*-(*p*-benzoxyphenylethyl)acetamido)oxazole, 87784-08-5; 2-(2-phenylvinyl)-5-[*N*-(*p*-benzoxyphenyl)methylcarbonyl]oxazole, 87784-09-6; 2-methyl-4-benzyl-5-oxazolone, 5469-44-3; α-isobutyl-α-aminoacetonitrile hydrochloride, 72177-82-3; α-benzyl-α-(acetylamino)acetonitrile, 24748-46-7; L-carbobenzyloxyglycylphenylalanine, 87784-10-9; L-*N*-cinnamoylleucine methyl ester, 87784-11-0; benzaldehyde, 100-52-7; L-phenylalanine, 63-91-2; benzylamine, 100-46-9; acetylglycine, 543-24-8.

Camphorae: Chiral Intermediates for the Enantiospecific Total Synthesis of Steroids. 1[1]

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Abstract: An enantiospecific approach to the total synthesis of cortisone and related steroids from readily available levorotatory borneol is presented.

It is not unjust to state that steroids are probably the single most intensely scrutinized class of natural products in the history of organic chemistry and that the science as a whole has been enriched by these studies. Nowhere is this more true than in the area of synthesis where many notable achievements have been forged out over the past 4 decades.[2] Many new strategies and methodological advances continue to be made in this area. As important as most of these advances have been, one crucial issue is often ignored and that is the question of stereochemistry—in the *absolute* sense. Since the biological activity of steroids is restricted to one enantiomer, a major problem has been the development of a practical method for the production of useful steroid intermediates in chirally pure form. A number of ingenious solutions to this important problem are now beginning to emerge. For example, the development and employment of remarkably efficient asymmetric induction reactions can be considered a major advance in this area.[3,4] Such methodology is clearly more ex-

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