Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidines. 4. Multiply-Substituted Aryl Derivatives

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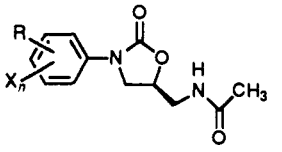
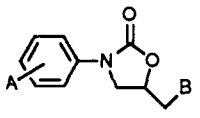
The synthesis and structure-activity relationship (SAR) studies of the effect of different polysubstitution patterns in the aromatic ring of 5-(acetamidomethyl)oxazolidinone antibacterials (I) on antibacterial activity are presented. Compounds I were prepared by the six-step synthesis described previously (Gregory, W. A.; et al. *J. Med. Chem.* 1989, *32*, 1673), electrophilic aromatic substitution reactions of 3-substituted compounds, and functional-group interchange reactions of 3,4-disubstituted compounds. Antibacterial evaluation of compounds I against *Staphylococcus aureus* and *Enterococcus faecalis* gave the following results. The 2,4- and 2,5-disubstituted derivatives have weak or no antibacterial activity. Antibacterial activities of 3,4-disubstituted compounds are comparable to those of the 4-monosubstituted analogues for small 3-substituents (smaller than Br), but decline rapidly for larger 3-substituents. 3,4-Annulated derivatives are comparable in activity to their open-chain analogues. 3,5-Disubstituted and 3,4,5- and 2,4,6-trisubstituted derivatives are devoid of antibacterial activity.

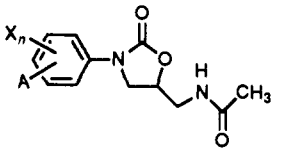


I

The oxazolidinones are a new class of orally active, synthetic antibacterial agents. In the preceding paper of this series[1] we described the synthesis and systematically examined the structure-activity relationships of the effect on antibacterial activity of varying the position of the "A" group in the aromatic ring of (acetamidomethyl)oxazolidinones (1). We concluded that 2-substituted compounds were inactive and that 3- and 4-substituted compounds possessed equivalent activity for small values of "A", but that the activity of 3-substituted compounds declined markedly for substituents larger than ethyl. We will now present an examination of the antibacterial activity of di- and trisubstituted phenyloxazolidinone acetamides (2).



1



2

Chemistry

A six-step synthesis (Scheme I) of 5-(acetamidomethyl)oxazolidinones has been reported previously.[2] The properties of compounds **3–13**, which were prepared by this route, are summarized in Table I.

The syntheses of compounds **14–17**,[2] **18–19**,[3] **20**,[1] and **22–34**[1] have already been described. The 2,4-dinitro derivative **21** was prepared by nitration of the parent phenyloxazolidinone.

Compounds with *o*-fluoro substituents required the specialized routes formulated in Scheme II. Transition metal-mediated cross-coupling[4] of TMS-acetylene with **5** afforded **35**, from which the protective group was cleaved to yield **36**. Hydration of the triple bond gave the desired acetyl compound **37**. The same sequence was employed to convert **6** into difluoro derivative **38**.

The 3-fluoro analogue was prepared by the modification of the standard six-step oxazolidinone synthesis outlined in Scheme III. 3-Fluoro-4-methylphenyl isocyanate was converted to the oxazolidinone tosylate **39** in the usual way (Scheme I). Oxidation of the methyl group of **39** was unsuccessful, but conversion of **39** to the bromide **40** followed by oxidation led smoothly to the acid **41**. Treatment of the acid chloride derived from **41** with dimethylcadmium[5] yielded acetophenone **42**, from which the remaining steps of the conventional oxazolidinone synthesis (Scheme I) proceeded uneventfully to yield the target **43**.

The remaining haloacetophenone derivatives were accessible through the key intermediate **47** (Scheme IV). Reduction of **20**[1] to the amine followed by trifluoroacetylation afforded **44**. Iodination of **44** proceeded smoothly without formation of undesired isomeric materials to yield **45**, which was converted to the protected *o*-amino acetophenone derivative **46** using the same sequence already described in Scheme II. Selective cleavage

† Chemical Sciences, Experimental Station.
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(1) Park, C.-H.; Brittelli, D. R.; Gregory, W. A.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidinones. 3. The Position of the "A" Group, unpublished results.
(2) Gregory, W. A.; Brittelli, D. R.; Wang, C.-L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Slee, A. M.; Forbes, M. Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidinones. 1. The Position of the "A" Group. *J. Med. Chem.* 1989, *32*, 1673–1681.
(3) Gregory, W. A.; Brittelli, D. R.; Wang, C.-L. J.; Kezar, III, H. S.; Carlson, R. K.; Park, C.-H.; Corless, P. F.; Miller, S. J.; Rajagopalan, P.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidinones. 2. The "A" Group. *J. Med. Chem.* 1990, *33*, 2569–2578.
(4) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Yau, K. S. Y. Facile Synthesis of Ethynylated Benzoic Acid Derivatives and Aromatic Compounds via Ethynyltrimethylsilane. *J. Org. Chem.* 1981, *46*, 2280–2286.
(5) Cason, J. The Use of Organocadmium Reagents for the Preparation of Ketones. *Chem. Rev.* 1947, *40*, 15–32.

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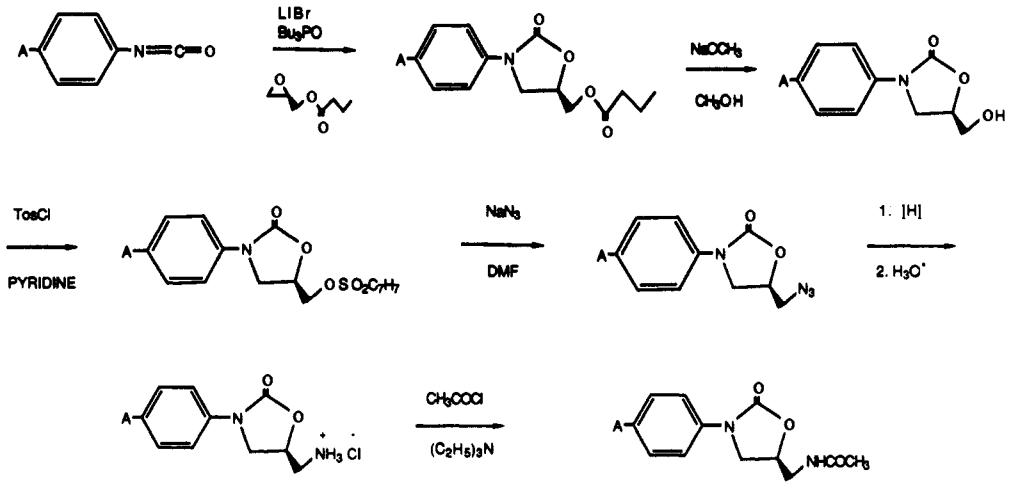
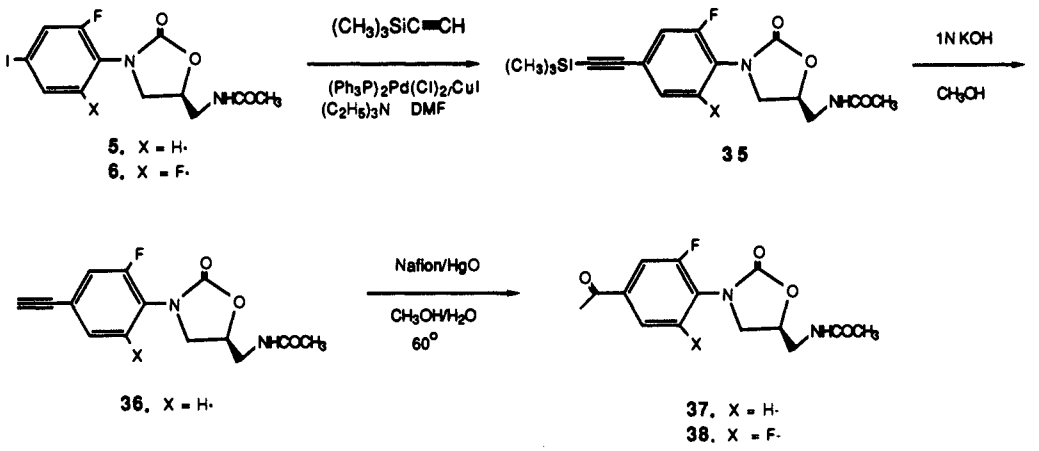
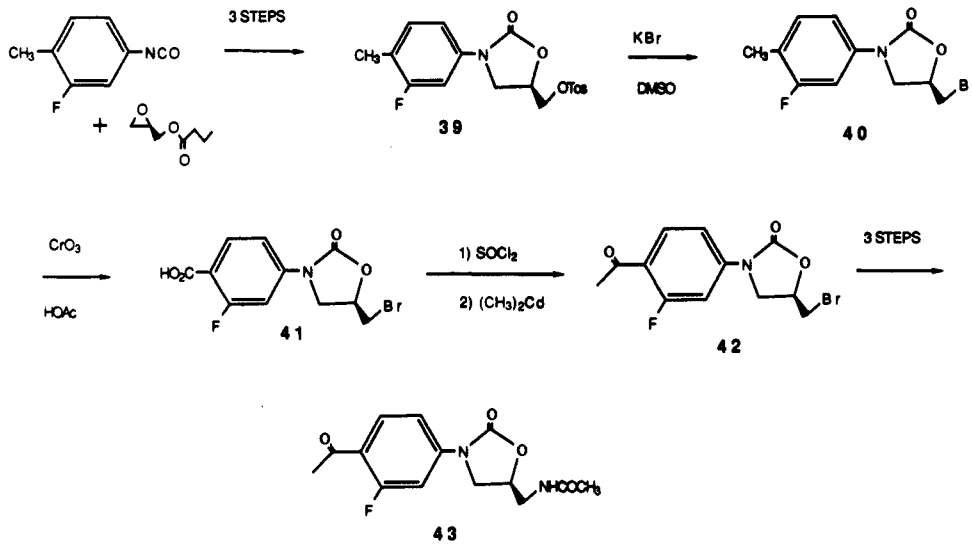
Scheme I



Scheme II



Scheme III



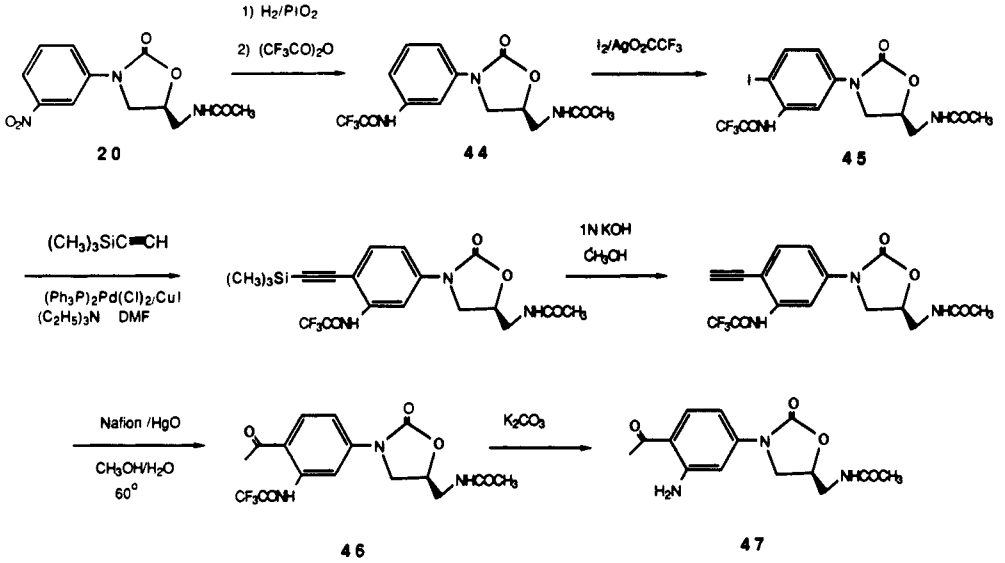
of the trifluoroacetyl group then afforded **47**. Sandmeyer reactions[6] of diazotized **47** gave the higher halo derivatives **48–50** (Scheme V). Schiemann reaction[7] of the diazo compound was unsuccessful, necessitating the alternative synthesis described in Scheme III.

Access to several 3,4-disubstituted compounds could readily be achieved simply by electrophilic aromatic substitution reactions of the corresponding 3-substituted compounds. Thus, acetophenones **51–56** were obtained free of undesired isomers simply by Friedel–Crafts acetylation of **23**, **28**, **30**, **31**, **34**, and **11** (Scheme VI). Regiochemistry was proved by observation of a nuclear Overhauser effect between acetyl methyl groups and these proton-bearing 3-substituents. The Friedel–Crafts ap-

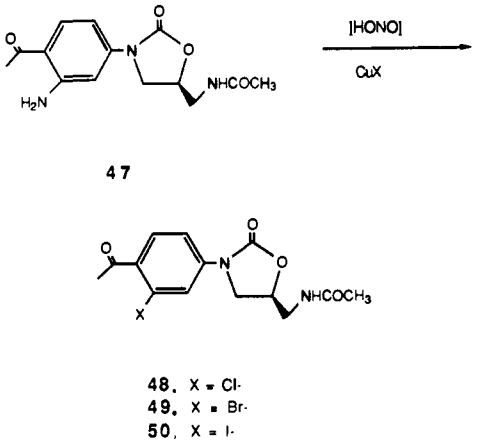
(6) Hodgson, H. H. The Sandmeyer Reaction. *Chem. Rev.* **1947**, *40*, 251–277. Cowdrey, W. A.; Davies, D. S. Sandmeyer and Related Reactions. *Q. Rev., Chem. Soc.* **1952**, *6*, 358–379.

(7) Roe, A. Preparation of Aromatic Fluorine Compounds from Diazonium Fluoborates: The Scheimann Reaction. In *Organic Reactions*; Adams, R., Ed.; John Wiley and Sons, Inc.: New York, 1949; pp 193–223.

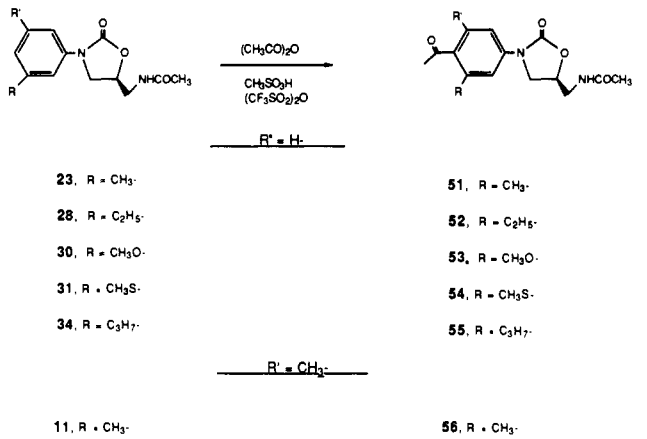
Scheme IV



Scheme V



Scheme VI



proach with 3-halo derivatives afforded isomeric mixtures of 3,4- and 2,5-disubstituted phenyloxazolidiones, hence the lengthy routes previously described. Chlorosulfonation of **23** also served as a useful route to sulfide **57** (Scheme VII).

Other compounds examined in this study were prepared by modifying substituents in the compounds whose syntheses have been described above. The phenol **58** was prepared by demethylation of **53** with boron tribromide. Sulfoxides **59–61** and sulfone **62** were prepared by oxidation of the corresponding sulfides under appropriate conditions. The indanone **63** resulted from chromic acid oxidation of **8** (Scheme VIII).

Structure–Activity Relationships

The in vitro antimicrobial activities of several representative meta- and para-substituted oxazolidinone acetamides which also bear ortho substituents are presented in Table II. Addition of an ortho substituent in **21**, **3**, and **4** eradicates the substantial (MIC = 2–4 μg/mL) activity[1] of the 3- and 4-monosubstituted nitro derivatives. The analogues **36** and **37** bearing the smaller ortho fluorine substituent retain some antimicrobial activity, but at much higher concentrations than their non-halogenated congeners.[2] We conclude that it is not profitable to seek improved antimicrobial activity in oxazolidinones by pursuing 2,4- and 2,5-disubstituted compounds.

A different picture emerges for 3,4-disubstituted derivatives, as can be seen from the effects of introducing substituents into the 3-position of the 4-acetyl compound **14**, presented in Table III. Activities of the corresponding 3-monosubstituted[3] compounds are provided for comparison so that the combined effects of the two substituents are more readily understood.

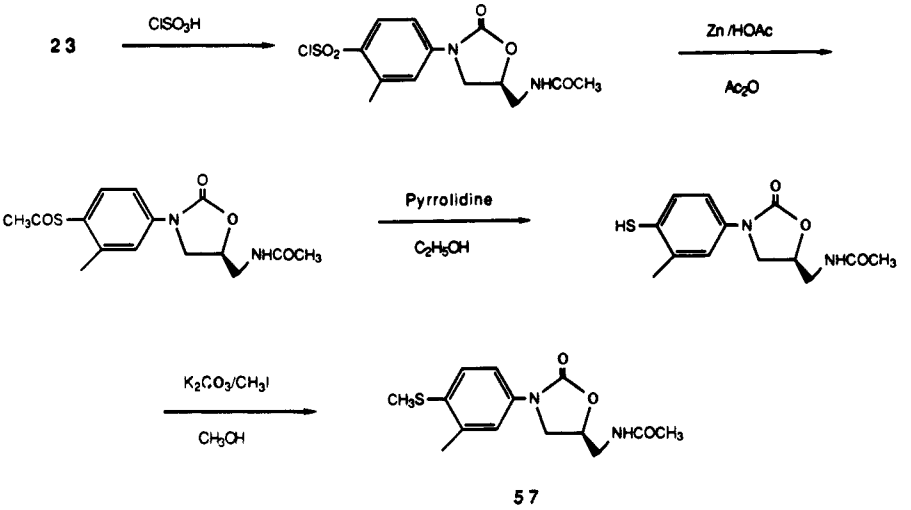
Adding the smallest substituents F, CH_3, HO, and Cl does not materially change the activity of the parent **14**. That the physicochemical properties of the acetyl group are responsible for the substantial antimicrobial activities of **43**, **51**, **58**, and **48** is evident by comparison with the MIC's of **15** and **22–25**.

As the size of 3-substituents increases beyond Cl, the level of antibacterial activity begins to drop off, equaling that of the weakly-active 3-monosubstituted compounds with X = C_2H_5 and I, and being nonexistent at concentrations tested with yet larger substituents. We would suggest that this is a size-related phenomenon, for introduction of these larger substituents destroys the activity of **14** irrespective of electronic character (electron-withdrawing or electron-donating) or lipophilicity (lipophilic or hydrophilic) of the added larger 3-substituents.

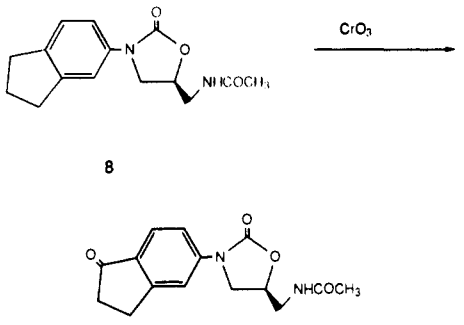
There also appears to be an interaction of size requirements between the 3- and 4-substituents. Compounds **53** and **54** are devoid of activity, in contrast to **30** and **31**, perhaps indicating that the presence of the acetyl group forces the methylchalcogenide substituents to adopt conformations which make the active site inaccessible.

Further elaborations of these themes are supported by the data in Table IV, in which it may be seen that the

Scheme VII



Scheme VIII



3-nitro group is also tolerated, being incorporated into 16 and 17 without reducing activity. The comparisons in this table also document more clearly the notion that the activity-conferring properties of 3- and 4-substituents are not additive, a conclusion particularly apparent from comparing the MIC's of 7 with 17 and 20 or 61 with 16 and 20.

The first five comparisons presented in Table V make it clear that conformationally restricting 3,4-substituents by tying them together to produce annulated derivatives offers no advantage in in vitro antimicrobial activity. The open-chain keto compounds 51 and 18 and their cyclized analogue with the same carbon atom content (63) are equipotent, and the same relationship holds for the hydrocarbon derivatives 8 and 19.

The drastic difference between the activities of the two 10-electron aromatic derivatives 9 and 10 is remarkable.

Surprising also is the total lack of antibacterial activity of the 3,5-disubstituted compounds 11 and 12 (Table VI); 11 could be expected to have at least modest activity on the basis of lipophilicity by comparison with its isomer 13. We would suggest that this observation might indicate that the site where oxazolidinones exert their action is rather narrow and possesses a pocket on only one side. A small meta substituent can be tolerated on one side (i.e., the 3-position) of the arene ring, but not both sides simultaneously.

Table VII explores two final substitution patterns. While introduction of one ortho-fluorine into 14 results in a substantial loss of potency, the two ortho-fluorines in 38 produce an analogue devoid of activity. And with the finding that the 3,5-disubstitution pattern of 11 is not tolerated, it is hardly surprising that the 3,4,5-trisubstituted derivative 56 is also devoid of antibacterial activity.

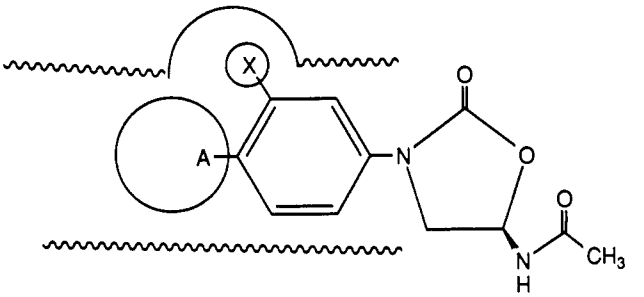


Figure 1.

Summary

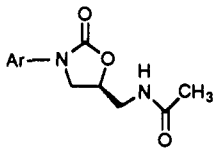
Several SAR generalization emerge from examination of polysubstituted *N*-phenyloxazolidinone acetamides. First, the 2-substituted compounds have, at best, weak activity. For substituents with small steric bulk, 3,4-disubstituted compounds have activity comparable to 4-monosubstituted compounds, but activity declines rapidly for larger 3-substituents. 3,4-Annulated derivatives are comparable in activity to their open-chain analogues. 3,5-Disubstituted and 3,4,5- and 2,4,6-trisubstituted derivatives are devoid of antibacterial activity. These generalizations are consistent with a requirement for coplanarity of the arene and oxazolidinone rings and with limited space available on one side of the aromatic ring away from the main axis of the phenyloxazolidinone pharmacophore (Figure 1).

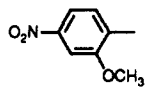
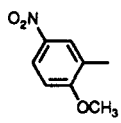
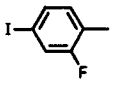
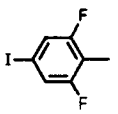
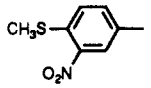
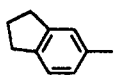
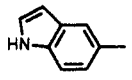
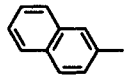
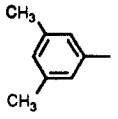
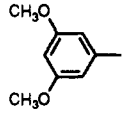
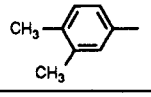
Experimental Section

A. Chemistry. Melting points were determined on Thomas-Hoover and Meltemp capillary and Buchi 510 automatic melting point apparatus and are uncorrected. Infrared spectra were recorded in KBr disks using Perkin-Elmer Model 21 or 137 spectrophotometers and are reported in reciprocal centimeters. ^{1}H NMR spectra were determined in the indicated solvent on IBM NR200-SY, General Electric QE-300, or Bruker WM-400 spectrometers and are reported in δ units (parts per million) downfield from tetramethylsilane as the internal reference. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were measured on VG ZAB-2F double focusing or Finnigan MAT Model 8230 high resolution mass spectrometers. Ultraviolet spectra were taken in absolute ethanol using a Cary 21 spectrophotometer.

The 5-(acetamidomethyl)oxazolidinones 3–13 were prepared according to the six-step synthesis of Scheme I previously described;[1] data on these compounds are presented in Table I. Syntheses of compounds 14–17,[2] 18 and 19,[3] 20,[1] and 22–34[1] have already been reported.

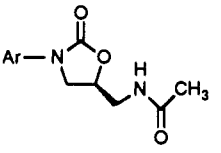
Table I. Physical Properties of Oxazolidinones Prepared According to Scheme I

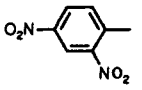
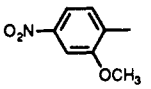
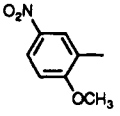
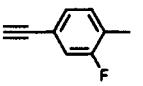
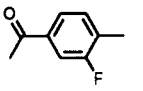


no.	Ar	mp, °C	formula	anal.
3		196–197	$C_{13}H_{15}N_3O_6$	C,H,N
4		141–143	$C_{13}H_{15}N_3O_6$	HRMS (HPLC)
5			$C_{12}H_{12}FIN_2O_3$	
6			$C_{12}H_{11}F_2IN_2O_3$	
7		176–178	$C_{13}H_{15}N_3O_5S$	C,H,N,S
8		131–133	$C_{15}H_{18}N_2O_3$	HRMS (HPLC)
9		209.5–210.5	$C_{14}H_{15}N_3O_3$	C,H,N
10		151.5–152.5	$C_{16}H_{16}N_2O_3$	C,H,N
11		153–155	$C_{14}H_{18}N_2O_3$	C,H,N
12		123–124	$C_{14}H_{18}N_2O_5$	C,H,N
13		122–124	$C_{14}H_{18}N_2O_3$	C,H,N

(*S*)-*N*-[[3-(2,4-Dinitrophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (21). To a solution of 11.0 g of potassium nitrate in 90 mL of concentrated sulfuric acid at 0 °C was added in portions 23.4 g (0.10 mol) of (*S*)-*N*-[[3-phenyl-2-oxo-5-oxazolidinyl]methyl]acetamide,[1] and the mixture was stirred at 0–10 °C for 1 h. An additional 3.0 g of potassium nitrate was then added, and the mixture was stirred for 2.0 h. Then the mixture was poured into an ice/water mixture, and the resulting precipitate was dissolved in $CHCl_3$. The supernate was extracted ten times with $CHCl_3$, and the combined organic solutions were evaporated in vacuo to yield 29.6 g of a mixture of crude products. The mixture was separated by preparative HPLC using 96:4 $CHCl_3/CH_3OH$ to yield 2.8 g (10%) of unreacted starting material, mp 130–131 °C, 6.3 g (23%) of (*S*)-*N*-[[3-(4-nitrophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide, mp 197–198 °C (lit.[2] mp 194.5–195.5 °C), and 16.0 g (49%) of **21**: mp 145–146 °C; $[\alpha]^{25}_D = -68.5 \pm 0.9°$ (c = 0.62, CH_3OH); ^1H NMR 200 MHz (DMSO-d_6) δ 1.88 (s, 3, CH_3CONH), 3.48 (t, *J* = 5 Hz, 2, CH_2NHAc), 4.00 (dd, *J* = 8, 5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.40 (dd, *J* = 8, 8 Hz, 1, C-4 *H* cis to C-5 *H*), 4.88 (m, 1, C-5 *H*), 7.83 (d, *J* = 10 Hz, 1, C-6′ H), 8.30 (m, 1, *H*NCOCH$_3$), 8.60 (dd, *J* = 10 Hz, *J*′ = 3 Hz, 1, C-5′ H), and 8.74 (d, *J* = 3 Hz, C-3′ H); IR (KBr) 3450, 3300, 1765, 1670, 1610, 1540, and 1345 cm^{-1}; UV (EtOH) λ_{max} (log ε) 217 (4.11) and 297 (3.89) nm. Anal. ($C_{12}H_{12}N_4O_7$) C, H, N.

Table II. Antibacterial Activities of 2,4- and 2,5-Disubstituted Phenyloxazolidinones



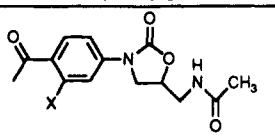
no.	Ar =	MIC, μg/mL *Staphylococcus aureus* SFCO-1a	MIC, μg/mL *Enterococcus faecalis* STCO-19
21		>128	>128
3		>128	>128
4		>128	>128
36		128	128
37		32	32

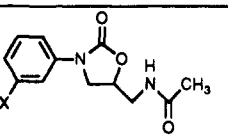
(*S*)-*N*-[[3-(4-Ethynyl-2-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (36). A. (*S*)-*N*-[[3-[4-[(Trimethylsilyl)ethynyl]-2-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (35). A mixture of 1.1 g (2.9 mmol) of **5**, 0.5 mL (3.5 mmol) of trimethylsilylacetylene, 40 mg (0.058 mmol) of bis(triphenylphosphine) palladium(II) chloride, and 10 mg (0.058 mmol) of copper(I) iodide in 3.5 mL of DMF and 2 mL of triethylamine was stirred at ambient temperature for 2.5 h. The solvent was removed in vacuo, and the residue was diluted with water and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give the crude product, which was purified by flash column chromatography to yield 0.92 g (91%) of **35**. ^1H NMR 200 MHz ($CDCl_3$) δ 0.23 (s, 9, $(CH_3)_3Si$), 2.00 (s, 3, CH_3CONH), 3.65 (t, *J* = 5 Hz, 2, CH_2NHAc), 3.80 (dd, *J* = 8, 5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.07 (dd, *J* = 7, 7 Hz, 1, C-4 *H cis* to C-5 *H*), 4.80 (m, 1, C-5 *H*), 6.33 (m, 1, *H*NCOCH$_3$), 7.22 (m, 2, C-5′ and C-6′ *H*'s) and 7.57 (t, 1, C-3′ *H*).

B. (*S*)-*N*-[[3-(4-Ethynyl-2-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (36). A solution of 0.850 g (2.44 mmol) of **35** in 20 mL of CH_3OH and 2 mL of 1 N aqueous potassium hydroxide solution was stirred at ambient temperature for 3 h and then neutralized with 10% aqueous hydrochloric acid. The CH_3OH was removed in vacuo, the residue was diluted with $CHCl_3$, and the resulting solution was washed with saturated aqueous sodium chloride solution. The separated $CHCl_3$ layer was dried ($MgSO_4$), and the crude product was purified by flash column chromatography, eluting with ethyl acetate to afford 0.450 g (67%) of **36**: mp 154–157 °C; HRMS (HPLC purity 90.6%); ^1H NMR 200 MHz (DMSO-d_6) δ 1.87 (s, 3, CH_3CONH), 3.43 (t, *J* = 5 Hz, 2, CH_2NHAc), 3.73 (dd, *J* = 8, 5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.10 (dd, *J* = 7, 7 Hz, 1, C-4 *H* cis to C-5 *H*), 4.37 (s, 1, acetylenic H), 4.77 (m, 1, C-5 *H*), 7.33–7.60 (m, 3, aromatic), and 8.27 (m, 1, *H*NCOCH$_3$); IR (Nujol mull) 1752 and 1657 cm^{-1}.

(*S*)-*N*-[[3-(4-Acetyl-2-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (37). A mixture of 0.430 g (1.55 mmol) of **36** and 0.450 g of Nafion/HgO in 5 mL of CH_3OH containing two drops of water was heated at 50–60 °C for 5 h. The catalyst was then filtered, and the CH_3OH was removed in vacuo. The

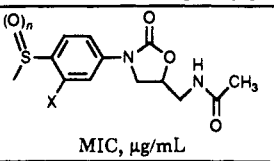
Table III. Antibacterial Activities of 3-Substituted 4-(Acetylphenyl)oxazolidinones

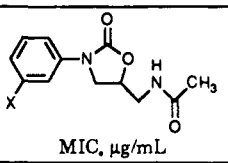




X	no.	MIC, μg/mL SFCO-1a	MIC, μg/mL STCO-19	no.	MIC, μg/mL SFCO-1a	MIC, μg/mL STCO-19
H	14	0.5	1	15	128	128
F	43	1	2	22	32	32
CH_3	51	1	1	23	32	32
HO	58	2	2	24	>128	>128
Cl	48	2	2	25	64	128
Br	49	4	8	18	16	64
H_2N	47	4	4	27	>128	>128
C_2H_5	52	16	8	28	16	16
I	50	32	32	29	64	128
CH_3O	53	>128	>128	30	64	64
CH_3S	54	>128	>128	31	16	16
CH_3SO	59	>128	>128	32	>128	>128
CH_3SO_2	62	>128	>128	33	>128	>128
n-C_3H_7	57	>128	>128	34	64	128

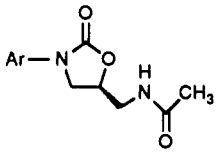
Table IV. Antibacterial Activities of [3-Substituted-4-(methylthio)phenyl]oxazolidinones





X	n	no.	MIC, μg/mL SFCO-1a	MIC, μg/mL STCO-19	no.	MIC, μg/mL SFCO-1a	MIC, μg/mL STCO-19
H	0	17	4	4			
	1	16	4	4			
CH_3	0	57	4	4	23	16	16
	1	60	8	8			
O_2N	0	7	8	8	20	4	4
	1	61	8	8			

Table V. Antibacterial Activities of Cyclic 3,4-Disubstituted Phenyloxazolidinones



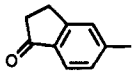
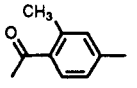
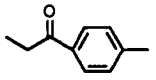
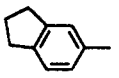
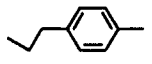
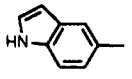
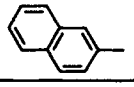
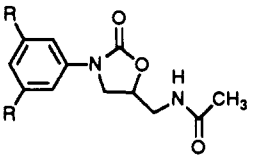
no.	Ar	MIC, μg/mL *Staphylococcus aureus* SFCO-1a	MIC, μg/mL *Enterococcus faecalis* STCO-19
63		2	2
51		1	1
18		0.5	1
8		2	4
19		2	4
9		>128	>128
10		4	8

Table VI. Antibacterial Activities of 3,5-Disubstituted Phenyloxazolidinones



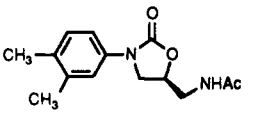
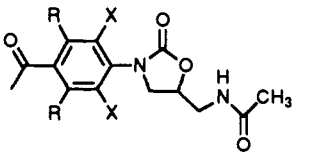
no.	R	MIC, μg/mL *Staphylococcus aureus* SFCO-1a	MIC, μg/mL *Enterococcus faecalis* STCO-19
11	CH_3	>128	>128
12	CH_3O	>128	>128
13		8	16

Table VII. Antibacterial Activities of Trisubstituted Phenyloxazolidinones



no.	R	X	MIC, μg/mL *Staphylococcus aureus* SFCO-1a	MIC, μg/mL *Enterococcus faecalis* STCO-19
38	H	F	>128	>128
57	CH_3	H	>128	>128

residue was dissolved in 10% CH_3OH/CH_2Cl_2, and the resulting solution was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$), and evaporated in vacuo to yield the crude product, which was purified by flash column chromatography, eluting with 2% CH_3OH/CH_2Cl_2 to give 0.380 g (83%) of **37**: mp 126–129 °C; HRMS (HPLC purity 90.5%); ^1H NMR 200 MHz ($CDCl_3$) δ 2.05 (s, 3, CH_3CONH), 2.63 (s, 3, CH_3CO), 3.70 (t, J = 5 Hz, 2, CH_2NHAc), 3.93 (dd, J = 8, 5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.18 (dd, J = 7, 7 Hz, 1, C-4 *H* cis to C-5 *H*), 4.88 (m, 1, C-5 *H*), 7.23 (m, 1, *H*NCOCH$_3$), and 7.63–7.83 (m, 3, aromatic-H); IR (Nujol mull) 1730, 1683, and 1671 cm^{-1}.

(*S*)-*N*-[[3-(4-Acetyl-2,6-difluorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (38). A. (*S*)-*N*-[[3-[4-[(Trimethylsilyl)ethynyl]-2,6-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. Using the same procedure described for preparation of **35**, 0.754 g (1.9 mmol) of **6** afforded 0.211 g (30%) of the title compound: ^1H NMR 200 MHz ($CDCl_3$) δ 0.23 (s, 9, $(CH_3)_3Si$), 2.00 (s, 3, CH_3CONH), 3.50 (t, J = 5 Hz, 2, CH_2NHAc), 3.83 (dd, J = 8, 5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.00 (dd, J = 7, 7 Hz), 1, C-4 *H* cis to C-5 *H*, 4.88 (m, 1, C-5 *H*), 6.52 (m, 1, *H*NCOCH$_3$), and 7.05 (d, J_{HF} = 10 Hz, 2, aromatic C-3′ and C-5′ *H*'s).

B. (*S*)-*N*-[[3-(4-Ethynyl-2,6-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide. Using the same procedure described for the preparation of **36**, 0.211 g (0.57 mmol) of the compound described in part A above afforded 0.167 g (100%) of the title compound: ^1H NMR 200 MHz ($CDCl_3$) δ 2.03 (s, 3, CH_3CONH), 3.23 (s, 1, acetylenic H), 3.50 (t, J = 5 Hz, 2, CH_2NHAc), 3.83 (dd, J = 8, 5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.00 (dd, J = 7, 7 Hz, 1, C-4 *H* cis to C-5 *H*), 4.92 (m, 1, C-5 *H*), 6.45 (m, 1, *H*NCOCH$_3$), and 7.11 (d, J_{HF} = 8 Hz, 2, aromatic).

C. (*S*)-*N*-[[3-(4-Acetyl-2,6-difluorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (38). Using the procedure described for the preparation of **37**, 0.211 g (0.57 mmol) of the compound described in part B above gave 0.098 g (56%) of **38**, mp 144–144.5 °C; HRMS (HPLC purity 95%); ^1H NMR 200 MHz ($CDCl_3$) δ 2.07 (s, 3, CH_3CONH), 2.62 (s, 3, CH_3CO), 3.50 (t, J = 5 Hz, 2, CH_2NHAc), 3.87 (dd, J = 8, 5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.08 (dd, J = 7, 7 Hz, 1, C-4 *H* cis to C-5 *H*), 4.95 (m, 1, C-5 *H*), 6.37 (m, 1, *H*NCOCH$_3$), and 7.57 (d, J_{HF} = 10 Hz, 2, aromatic-H); IR (CH_2Cl_2) 1770, 1696, and 1682 cm^{-1}.

(*S*)-*N*-[[3-(4-Acetyl-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (43). A. (*S*)-[3-(4-Methyl-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl Bromide (40). To a solution of 30 g (82 mmol) of (*S*)-*N*-[3-(4-methyl-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl bromide (**39**) (prepared from 4-methyl-3-fluorophenyl isocyanate using the first three steps of the general oxazolidinone synthesis (Scheme I), mp 144–145.5 °C) in 100 mL of DMF was added 0.5 g of 18-crown-6 and 20 g (168 mmol) of potassium bromide, and the mixture was heated at 70 °C for 18 h. The solvent was removed in vacuo, and the product was triturated with water, filtered, and dried to yield 22.3 g (94.5%) of **40**: mp 104–107 °C, 97% pure by HPLC; ^1H NMR 300 MHz ($CDCl_3$) δ 2.25 (d, J_{HF} = 2 Hz, 3, CH_3), 3.57 and 3.63 (d of AB, J_{AB} = 11 Hz, J = 7.5 Hz, J' = 4 Hz, 2, CH_2Br), 3.88 (dd, J = 9, 6 Hz), 1, C-4 *H* trans to C-5 *H*), 4.14 (dd, J = 9, 9 Hz), 1, C-4 *H* cis to C-5 *H*, 4.87 (m, 1, C-5 *H*), and 7.13, 7.17, and 7.37 (ABC, J_{AB} = 8 Hz, J_{BC} = 2 Hz, J_{HF} = 12 Hz, 3, C-6′, C-2′, and C-5′ H's, respectively).

B. (*S*)-[3-(4-Carboxy-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl Bromide (41). A solution of 6.0 g (20 mmol) of **40** in 50 mL of acetic acid and 14.4 mL of acetic anhydride was cooled to 0 °C and treated dropwise with a solution of 14.4 g of chromium(VI) oxide in 11 mL of water and 43 mL of acetic acid at 10–15 °C. After 2 h the mixture was allowed to warm to ambient temperature and was stirred at that temperature for 4 h. The mixture was then poured into 1200 mL of ice/water mixture and stirred overnight. The insoluble material was filtered and dried to afford 4.2 g of crude **41**, which was purified by dissolving in excess aqueous sodium bicarbonate solution, filtering to remove insoluble material, and acidifying to yield 2.07 g of **41** (31%): mp 212–214 °C; ^1H NMR 360 MHz (DMSO-d_6) δ 3.80–3.95 (m, 3, CH_2Br and C-4 *H* trans to C-5 *H*), 4.30 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 H), 5.03 (m, 1, C-5 H), 7.44, 7.58, and 7.91 (ABC, J_{AB} = 1.7 Hz, J_{AC} = 7.5 Hz, J_{HBF} = 11.5 Hz, J_{HCF} = 7.5 Hz, C-6′, C-2′, and C-5′ H, respectively), and 13.1 (br, 1, CO_2H).

C. (*S*)-*N*-[[3-(4-Acetyl-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (43). A solution of 6.62 g (20.8 mmol) of **41** in 100 mL of THF was treated with 5 mL (68.5 mmol) of thionyl chloride and heated under reflux for 3 h. The solvent was removed in vacuo, and the residue was dissolved in 100 mL of dry benzene, treated with 10 g of dimethylcadmium, heated under reflux for 3.5 h, and then allowed to stir at ambient temperature for 18 h. The resulting mixture was diluted with 30 mL of $CHCl_3$, cooled to 10 °C, and treated with 20 mL of water. The mixture was stirred at ambient temperature until gas (methane) evolution ceased. The mixture was then filtered (the solid was washed with $CHCl_3$), and the organic layer of the filtrate was dried ($MgSO_4$) and evaporated in vacuo. The resulting solid was dissolved in 200 mL of $CHCl_3$, and the solution was washed twice with 1 N aqueous hydrochloric acid, twice with water, once with 5% sodium bicarbonate solution, twice with water, and once with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated in vacuo to afford 5.0 g of **42**, which was purified by preparative HPLC to give 3.4 g (52%) of **42**, which was 95% pure by HPLC. Bromide **42** was converted to the corresponding acetamide using the final steps of the usual synthesis (Scheme I) to afford 2.31 g (73%) of **43**: mp 173.5–174.5 °C; $[\alpha]^{25}_D$ = −46.7 ± 0.8° (c = 0.91, acetonitrile); ^1H NMR 300 MHz ($CDCl_3$) δ 2.03 (s, 3, CH_3CONH), 2.61 (d, J_{HF} = 5 Hz, 3, CH_3CO), 3.66 (m, 2, CH_2NHAc), 3.83 (dd, J = 9, 7 Hz, 1, C-4 *H* trans to C-5 *H*), 4.09 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.81 (m, 1, C-5 *H*), 6.21 (t, J = 7 Hz, 1, *H*NCOCH$_3$), and 7.20, 7.56, and 7.92 (ABC, J_{AC} = 8 Hz, J_{AB} = 2 Hz, J_{HBF} = 13 Hz, J_{HCF} = 8 Hz, 3, aromatic C-6′, C-2′, and C-5′-H's, respectively). Anal. ($C_{14}H_{15}FN_2O_4$) C, H, N, F.

(*S*)-*N*-[[3-[3-(Trifluoroacetamido)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (44). A mixture of 18.6 g (66.6 mmol) of **20**,[1] 1.0 g of platinum(IV) oxide, and 200 mL of 95% ethanol was treated with 45 psi of hydrogen in a Parr apparatus until hydrogen uptake ceased. The solvent was removed *in vacuo* to yield 16.6 g (100%) of the amine, which was homogenous by HPLC. A solution of 33.2 g (133 mmol) of this amine in 300 mL of THF containing 26 mL (a 40% excess) of triethylamine was maintained at 5–10 °C as a solution of 21 mL of trifluoroacetic anhydride in 30 mL of THF was added dropwise. The mixture was then allowed to warm to ambient temperature, the solvent was removed in vacuo, and the residue was triturated with water, filtered, and dried to yield 25 g of product which was 82% pure. The solid was triturated three times with 400 mL of warm $CHCl_3$ to remove a soluble impurity, affording 18.5 g (40%) of **44**: mp 149–150 °C; ^1H NMR 300 MHz (CD_3CN) δ 1.93 (s, 3, CH_3CONH), 3.57 (m, 2, CH_2NHAc), 3.79 (dd, J = 9, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 4.10 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.77 (m, 1, C-5 *H*), 6.80 (br, 1, *H*NCOCH$_3$), 7.35–7.50 (m, 4, aromatic *H*), and 8.05 (br, 1, CF_3CONH).

(*S*)-*N*-[[3-[4-Iodo-3-(trifluoroacetamido)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (45). To a mixture of 18.5 g (53.6 mmol) of **44** and 13.0 g (59 mmol) of silver trifluoroacetate in 500 mL of acetonitrile was added in several portions 13.6 g (53.6 mmol) of iodine. After 1.0 h, another 1.2 g of the silver salt was added, and the mixture was stirred for 4 h. The reaction was still not complete, so an additional 2.4 g of silver trifluoroacetate and 0.7 g of iodine were added, and the mixture was stirred for 17 h. Then, 1.2 g of silver trifluoroacetate and 0.5 g of iodine were added, and the mixture was stirred for 5 h. The mixture was then filtered, and filtrate was evaporated in vacuo, and the product was triturated with water, filtered, and vacuum-dried at 110 °C to yield 25.5 g (100%) of **45** which was 97% pure by HPLC.

(*S*)-*N*-[[3-(4-Acetyl-3-acetamidophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (47). A. (*S*)-*N*-[[3-[4-[(Trimethylsilyl)ethynyl]-3-(trifluoroacetamido)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. Using the same procedure described for preparation of **35**, 27.5 g (58.4 mmol) of **45** afforded 17 g (66%) of the title compound: ^1H NMR 400 MHz ($CDCl_3$) δ 0.28 (s, 9, $(CH_3)_3Si$), 2.01 (s, 3, CH_3CONH), 3.75 (m, 2, CH_2NHAc), 3.79 (dd, J = 8, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 4.11 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.80 (m, 1, C-5 *H*), 6.21 (m, 1, *H*NCOCH$_3$), 7.45, 7.61, and 8.37 (ABC, J_{AB} = 9 Hz, J_{BC} = 2 Hz, 3, aromatic C-6′, C-5′, and C-2′ *H*'s, respectively, and 8.86 (br, 1, CF_3CONH).

B. (*S*)-*N*-[[3-[4-Ethynyl-3-(trifluoroacetamido)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. Using the

same procedure described for the preparation of **36**, 17.0 g (38.5 mmol) of the compound described in part A above afforded the title compound.

C. (*S*)-*N*-[[3-[4-Acetyl-3-(trifluoroacetamido)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (46). Using the procedure described for the preparation of **38**, the compound described in part B above gave **46**.

D. (*S*)-*N*-[[3-(4-Acetyl-3-aminophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (47). The mixture of crude **46** from part C above in 700 mL of CH_3OH was treated with a solution of 2.5 g (40 mmol) of potassium carbonate in 30 mL of water and heated under reflux for 5 h. The solvents were removed in vacuo, and the residue was triturated with two 400-mL portions of acetonitrile, which were filtered to remove insoluble material and evaporated in vacuo to yield 10.7 g (95% from **45**) of **47**: mp 166.5–169 °C; $[\alpha]^{25}_D = -32.4 \pm 0.8°$ (c = 1.02, CH_3OH). ^1H NMR 400 MHz (CD_3CN) δ 1.98 (s, 3, CH_3CONH), 2.58 (s, 3, CH_3CO), 3.62 (m, 2, CH_2NHAc), 3.83 (dd, J = 8, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 4.15 (dd, J = 8, 8 Hz, 1, C-4 *H* cis to C-5 *H*), 4.81 (m, 1, C-5 *H*), 6.78 (br, 3, $HNCOCH_3$ and NH_2), 6.96–7.03 (m, 2, C-6′ and C-2′ H) and 7.86 (d, $J_{5',6'}$ = 7 Hz, 1, C-5′ H). Anal. ($C_{14}H_{17}N_3O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Acetyl-3-chlorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (48). To a solution of 1.1 g (3.8 mmol) of **47** in 4 mL of water and 0.75 mL of 12 N hydrochloric acid at 0 °C was added 0.27 g of sodium nitrite in 1 mL of water. The mixture was stirred briefly, then adjusted to pH 4 with solid sodium bicarbonate, and added to a solution of 0.5 g of copper(I) chloride in 7 mL of water (containing enough hydrochloric acid to dissolve the copper salt) and 7 mL of acetonitrile at 50–60 °C. The mixture was diluted with 30 mL of water, and the acetonitrile was removed in vacuo. The mixture was extracted with $CHCl_3$, and the $CHCl_3$ layer was dried ($MgSO_4$) and evaporated in vacuo to yield 0.72 g (61%) of **48**, which was crystallized from *n*-butyl chloride to afford 0.19 g (16%) of pure **48**: mp 133–134 °C; $[\alpha]^{25}_D = -30.2 \pm 1.0°$ (c = 0.82, CH_3OH); ^1H NMR 360 MHz (CD_3CN) δ 1.90 (s, 3, CH_3CONH), 2.61 (s, 3, CH_3CO), 3.55 (m, 2, CH_2NHAc), 3.80 (dd, J = 9, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 4.12 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.78 (m, 1, C-5 *H*), 6.73 (br, 1, $HNCOCH_3$), and 6.56, 7.77, and 7.78 (ABC, J_{AC} = 2 Hz, J_{AB} = 2 Hz, 3, C-6′, C-5′, and C-2′ *H*'s, respectively). Anal. ($C_{14}H_{15}ClN_2O_4$) C, H, N, Cl.

(*S*)-*N*-[[3-(4-Acetyl-3-bromophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (49). Using the same procedure described for the preparation of **48** above, 0.93 g (3.2 mmol) of **47** and 0.6 g of copper(I) bromide afforded 0.21 g (18%) of **49**: mp 116–117 °C; $[\alpha]^{25}_D = -25.5 \pm 0.8°$ (c = 1.00, CH_3OH); ^1H NMR 360 MHz ($CDCl_3$) δ 2.03 (s, 3, CH_3CONH), 2.63 (s, 3, CH_3CO), 3.68 (m, 2, CH_2NHAc), 3.81 (dd, J = 9, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 4.08 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.82 (m, 1, C-5 *H*), 6.11 (br, 1, $HNCOCH_3$), 7.58 (s, 2, C-5′ and C-6′ H's) and 7.81 (d, J = 2 Hz, 1, C-2′ *H*). Anal. ($C_{14}H_{15}BrN_2O_4$) C, H, N, Br.

(*S*)-*N*-[[3-(4-Acetyl-3-iodophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (50). Using the same procedure described for the preparation of **48** above, 1.1 g (3.8 mmol) of **47**, 0.8 g of potassium iodide, and 0.10 g of copper(I) iodide afforded 0.81 g (53%) of **50**: mp 68 °C dec; $[\alpha]^{25}_D = -16.8 \pm 1.1°$ (*c* = 0.75, 25% acetonitrile in CH_3OH); ^1H NMR 360 MHz (CD_3CN) δ 1.91 (s, 3, CH_3CONH), 2.58 (s, 3, CH_3CO), 3.55 (m, 2, CH_2NHAc), 3.80 (dd, J = 9, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 4.10 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.78 (m, 1, C-5 *H*), 6.75 (br, 1, $HNCOCH_3$), and 7.65, 7.75, and 8.27 (ABC, J_{AB} = 10 Hz, J_{AC} = 2 Hz, 3, C-6′, C-5′, and C-2′ *H*'s, respectively).

(*S*)-*N*-[[3-(3-Methyl-4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (51). To 3.0 mL of acetic anhydride and 30 mL of methanesulfonic acid was added 3.0 g (12 mmol) of **23**,[1] the mixture was stirred for 4 h and then poured into 170 mL of ice/water, and the pH was adjusted to 7.5 with ammonium hydroxide solution. The solid which formed was filtered, washed with water, and dried to yield 2.64 g of **51**, which was crystallized from *n*-butyl chloride to afford 1.50 g (43%) of **51**: mp 134–135 °C; $[\alpha]^{25}_D = -31.9 \pm 0.8°$ (c = 1.99, CH_3OH); ^1H NMR 360 MHz ($CDCl_3$) δ 2.03 (s, 3, CH_3CONH), 2.57 (s, 3, CH_3-Ar), 2.57 (s, 3, CH_3CO), 3.68 (m, 2, CH_2NHAc), 3.83 (dd, J = 9, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 4.09 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.80 (m, 1, C-5 *H*), 6.19 (t, 1, J = 6 Hz, $HNCOCH_3$), and 7.33, 7.51, and 7.76 (ABC, J_{AB} = 2 Hz, J_{BC} = 10 Hz, 3, C-2′, C-6′, and C-5′ *H*'s, respectively). Anal. ($C_{15}H_{18}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-(3-Ethyl-4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (52). Using the same procedure described above for the preparation of **51**, 3.0 g (11 mmol) of **28**[1] afforded 2.8 g (80%) of **52**: mp 90–91 °C; $[\alpha]^{25}_D = -28.5 \pm 0.8°$ (c = 2.01, CH_3OH); ^1H NMR 360 MHz ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3, CH_3CH_2), 2.03 (s, 3, CH_3CONH), 2.57 (s, 3, CH_3CO), 2.92 (q, J = 7 Hz, 2, CH_3CH_2), 3.67 (m, 2, CH_2NHAc), 3.83 (dd, J = 9, 7 Hz, 1, C-4 *H* trans to C-5 *H*), 4.10 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.81 (m, 1, C-5 *H*), 6.49 (br t, 1, J = 6 Hz, $HNCOCH_3$), and 7.37, 7.46, and 7.69 (ABC, J_{AB} = 2 Hz, J_{BC} = 9 Hz), 3, C-2′, C-6′, and C-5′ *H*'s, respectively). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-(3-Methoxy-4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (53). Using the same procedure described above for the preparation of **51**, 3.0 g (11 mmol) of **30**[1] afforded 2.0 g (57%) of **53**: mp 200–202 °C; $[\alpha]^{25}_D = -40.8 \pm 0.8°$ (c = 1.01, acetonitrile); ^1H NMR 360 MHz ($CDCl_3$) δ 2.03 (s, 3, CH_3CONH), 2.60 (s, 3, CH_3CO), 3.68 (m, 2, CH_2NHAc), 3.82 (dd, J = 9, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 3.93 (s, 3, CH_3O), 4.10 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.80 (m, 1, C-5 *H*), 6.14 (br t, J = 6 Hz, 1, $HNCOCH_3$), and 6.77, 7.64, and 7.81 (ABC, J_{AB} = 2 Hz, J_{AC} = 9 Hz, 3, C-6′, C-2′, and C-5′ *H*'s, respectively). Anal. ($C_{15}H_{18}N_2O_5$) C, H, N.

(*S*)-*N*-[[3-[3-(Methylthio)-4-acetylphenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (54). Using the same procedure described above for the preparation of **12**, 3.0 g (10.7 mmol) of **31**[1] afforded 1.90 g (54%) of **54**, mp 187.5–188.5 °C; $[\alpha]^{25}_D = -37.3 \pm 0.8°$ (c = 1.00, acetonitrile); ^1H NMR 360 MHz ($CDCl_3$) δ 2.04 (s, 3, CH_3CONH), 2.43 (s, 3, CH_3S), 2.60 (s, 3, CH_3CO), 3.69 (m, 2, CH_2NHAc), 3.87 (dd, J = 9, 7 Hz, 1, C-4 *H* trans to C-5 *H*), 4.11 (dd, J = 9, 9 Hz), 1, C-4 *H* cis to C-5 *H*), 4.82 (m, 1, C-5 *H*), 6.11 (m, 1, $HNCOCH_3$), and 7.12, 7.74, and 7.86 (ABC, J_{AB} = 2 Hz, J_{AC} = 9 Hz), 3, C-6′, C-2′, and C-5′ H's, respectively). Anal. ($C_{15}H_{18}N_2O_4S$) C, H, N, S.

(*S*)-*N*-[[3-(3-*n*-Propyl-4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (55). Using the same procedure described above for the preparation of **51**, 3.0 g (10.8 mmol) of **34**[1] afforded 1.68 g (56%) of **55**: mp 114.5–115.5 °C; ^1H NMR 300 MHz ($CDCl_3$) δ 0.96 (t, (J = 7 Hz), 3, $CH_3CH_2CH_2$), 1.58 (sextet, J = 7 Hz, 2, $CH_3CH_2CH_2$), 2.02 (s, 3, CH_3CONH), 2.58 (s, 3, CH_3CO), 2.87 (t, J = 7 Hz, 2, $CH_3CH_2CH_2$), 3.70 (m, 2, CH_2NHAc), 3.85 (dd, J = 9, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 4.09 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.80 (m, 1, C-5 *H*), 6.20 (m, 1, $HNCOCH_3$), and 7.36, 7.49, and 7.71 (ABC, J_{AB} = 2 Hz, J_{BC} = 10 Hz, 3, C-2′, C-6′, and C-5′ H's, respectively). Anal. ($C_{17}H_{22}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-(3,5-Dimethyl-4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (56). To 1.01 g (3.9 mmol) of **11** in 10 mL of methanesulfonic acid was added by pipette 1.0 mL (11 mmol) of acetic anhydride, the mixture was stirred for 2.0 h, then poured into ice/water, and stirred, and the solid which formed was filtered and dissolved in ethyl acetate. The ethyl acetate solution was dried ($MgSO_4$) and evaporated in vacuo to yield 1.10 g (94%), which was crystallized from *n*-butyl chloride to give 0.321 g (27%) of **56**, mp 136–138 °C; $[\alpha]^{25}_D = -23.3 \pm 2.0°$ (c = 1.03, CH_3OH); ^1H NMR 300 MHz ($CDCl_3$) δ 2.03 (s, 3, CH_3CONH), 2.25 (s, 6, CH_3-Ar), 2.46 (s, 3, CH_3CO), 3.62 (t, J = 5 Hz, 2, CH_2NHAc), 3.78 (dd, J = 9, 7 Hz, 1, C-4 *H* trans to C-5 *H*), 4.03 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.78 (m, 1, C-5 *H*), 6.64 (t, 1, J = 6 Hz, $HNCOCH_3$), and 7.18 (2, s, C-3′ and C-5′ *H*'s); IR (KBr) 3340, 1750, 1662, and 1609 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 241 (4.03) nm. Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[3-Methyl-4-(methylthio)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (57). A. (*S*)-*N*-[[3-[3-Methyl-4-(chlorosulfonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. To 20 mL of chlorosulfuric acid under nitrogen in an ice bath was added, in small portions, so that the temperature stayed between 5 and 10 °C, 4.9 g (20 mmol) of **23**.[3] The solution was allowed to stir at 10 °C for 1.0 h, and then it was poured onto 350 mL of ice with stirring. After the ice melted, the product was filtered and dissolved in ethyl acetate, and the ethyl acetate solution was dried ($MgSO_4$) and evaporated in vacuo to yield 4.11 g (60%) of the title compound: ^1H NMR 300 MHz (DMSO-d_6) δ 1.85 (s, 3, CH_3CONH), 2.55 (s, 3, CH_3-Ar), 3.42 (m, 2, CH_2NHAc), 3.77 (m, 1, C-4 *H* trans to C-5 *H*), 4.12 (dd, J = J' = 9.5 Hz, 1,

C-4 *H* cis to C-5 *H*), 4.73 (m, 1, C-5 *H*), 7.34 and 7.73 (AB, J_{AB} = 9 Hz, 2, C'6 and C'-5 H's, respectively), 7.35 (s, 1, C'-2 H), and 8.35 (t, 1, *J* = 6 Hz, *H*NCOCH$_3$).

B. (*S*)-*N*-[[3-[3-Methyl-4-(acetylthio)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. To a solution of 4.11 g (11.9 mol) of the compound described in part A above in 50 mL of acetic acid were added 17 mL of acetic anhydride and 5 g of anhydrous sodium acetate, and the mixture was stirred well as 4 g of zinc dust was added. The mixture was refluxed for 1.0 h, then cooled, and filtered, and the solvent was removed in vacuo. The residue was triturated with water and filtered to give the product, 3.01 g (79%): ^{1}H NMR 300 MHz (DMSO-d_6) δ 1.85 (s, 3, C*H*$_3$CONH), 2.28 (s, 3, C*H*$_3$-Ar), 2.42 (s, 3, C*H*$_3$COS), 3.43 (dd, *J* = *J'* = 5 Hz, 2, C*H*$_2$NHAc), 3.77 (dd, *J* = 6 Hz, *J'* = 9.5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.13 (dd, *J* = *J'* = 9.5 Hz, 1, C-4 *H* cis to C-5 *H*), 4.74 (m, 1, C-5 *H*), 7.37 and 7.52 (AB, J_{AB} = 8 Hz, 2, C'6 and C'-5 H's, respectively), 7.53 (s, 1, C'-2 H) and 8.27 (t, 1, *J* = 6 Hz, *H*NCOCH$_3$).

C. (*S*)-*N*-[[3-(3-Methyl-4-mercaptophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide. To a suspension of 2.99 g (9.3 mmol) of the compound described in part **B** above in 20 mL of absolute ethanol under nitrogen was added 3.0 mL of pyrrolidine. The mixture became warm, and all the material dissolved. The mixture was stirred until the starting material had been consumed (TLC), then the solvent was removed in vacuo, and the resulting residue was triturated with water. The aqueous suspension was acidified by addition of a little acetic acid and then chilled, and the product was filtered to give 2.60 g (100%).

D. (*S*)-*N*-[[3-[3-Methyl-4-(methylthio)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (57). To 0.40 g (11 mmol) of sodium hydroxide and 0.70 mL (11 mmol) of methyl iodide in 25 mL of ethanol under nitrogen were added 2.80 g (10 mmol) of the compound described in part C above and 5 mL of water, and the mixture was stirred under nitrogen for 18 h. The solution was then evaporated in vacuo, and the residue was triturated with water and filtered to yield 1.82 g of product containing some unalkylated mercaptan. The sample was exhaustively extracted with boiling *n*-butyl chloride to give a clear solution which upon concentration and cooling deposited 1.6 g (54%) of **57**. This material was recrystallized from CH$_3$OH to afford 0.554 g: mp 152.5–153.5 °C; $[\alpha]^{25}_D$ = −23.0° (*c* = 0.65, CH$_3$OH); ^{1}H NMR 360 MHz (DMSO-d_6) δ 1.83 (s, 3, C*H*$_3$CONH), 2.27 (s, 3, C*H*$_3$-Ar), 2.43 (s, 3, C*H*$_3$S), 3.42 (m, 2, C*H*$_2$NHAc), 3.72 (dd, *J* = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.08 (dd, *J* = 8, 8 Hz, 1, C-4 *H* cis to C-5 *H*), 4.71 (m, 1, C-5 *H*), 7.23 and 7.39 (AB, J_{AB} = 6 Hz, 2, aromatic C-6' and C-5' H, respectively), 7.36 (s, 1 C-2' H), and 8.24 (t, 1, *J* = 6 Hz, *H*NCOCH$_3$); IR (KBr) 3300, 1750, 1650, and 1600 cm^{-1}; UV (EtOH) λ_{max} (log ε) 265 (4.29) nm. Anal. ($C_{14}H_{18}N_2O_3S$) C, H, N, S.

(*S*)-*N*-[[3-(3-Hydroxy-4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (58). A solution of 1.0 g (3.26 mmol) of **53** in 130 mL of CH_2Cl_2 was cooled to −78 °C under nitrogen and 4.5 mL (4.5 mmol) of a 1.0 N solution of boron tribromide in CH_2Cl_2 was added. The mixture was allowed to warm to ambient temperature and stirred for 18 h. The resulting mixture was cooled to −20 °C and treated with 2 mL of water. Solvents were then removed in vacuo to yield a red-black liquid. The liquid was treated with 30 mL of water, the pH was adjusted to 7 by addition of 10% aqueous hydrochloric acid solution, and the solid which resulted was filtered. Crystallization and recrystallization from *n*-butyl chloride afforded 0.070 g (7%) of **58**: mp 185.5–187 °C; ^{1}H NMR 360 MHz (CDCl$_3$) δ 2.03 (s, 3, C*H*$_3$CONH), 2.60 (s, 3, C*H*$_3$CO), 3.68 (m, 2, C*H*$_2$NHAc), 3.79 (dd, *J* = 9, 6 Hz, 1, C-4 *H* trans to C-5 *H*), 4.08 (dd, *J* = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.80 (m, 1, C-5 *H*), 6.08 (br, 1, *H*NCOCH$_3$), 6.93, 7.34, and 7.72 (ABC, J_{AB} = 2 Hz, J_{AC} = 9 Hz, 3, C-2', C-6', and C-5' H's, respectively), and 12.50 (s, 1, O*H*).

(*S*)-*N*-[[3-[3-(Methylsulfinyl)-4-acetylphenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (59). To a solution of 4.56 g (10.7 mmol) of **54** in 100 mL of CHCl$_3$ was added 2.0 g (10 mmol) of 85% *m*-chloroperbenzoic acid in small portions. The mixture was washed with 10% aqueous sodium thiosulfate solution, dried (MgSO$_4$), and evaporated in vacuo. The resulting semisolid was triturated with two 100-mL portions of diethyl ether, and the insoluble material was crystallized from CHCl$_3$ to afford 1.70 g (47%) of **59** as a mixture of diastereomers: mp 174–202 °C dec; $[\alpha]^{25}_D$ = −44.5 ± 0.4° (*c* = 2.01, CH$_3$OH); ^{1}H NMR 360 MHz (CDCl$_3$) δ 2.03 (s, 3, C*H*$_3$CONH), 2.64 (s, 3, C*H*$_3$CO), 2.81 (s, 3, C*H*$_3$S), 3.68 (m, 2, C*H*$_2$NHAc), 3.96 (dd, *J* = 9, 7 Hz, 1, C-4 *H* trans to C-5 *H*), 4.26 (dd, *J* = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.88 (m, 1, C-5 *H*), 6.60 (m, 1, *H*NCOCH$_3$), 7.98 (d, J = 2 Hz, 1, C-6') and 8.05–8.25 (m, 2, C-5', and C-2' H's). Anal. ($C_{15}H_{18}N_2O_5S$) C, H, N, S.

(*S*)-*N*-[[3-[3-Methyl-4-(methylsulfinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (60). To a suspension of 1.35 g (4.6 mmol) of **57** in 100 mL of 1:1 CH_2Cl_2/CHCl$_3$ at 5–10 °C under nitrogen was added 0.79 g (4.6 mmol) of *m*-chloroperbenzoic acid. The mixture was then stirred for 20 min at 10 °C, and then 3 mL of dimethyl sulfide was added to consume unreacted oxidant. The mixture was then evaporated to dryness in vacuo, and the residue was triturated with 100 mL of ether under nitrogen for 18 h. The resulting crystalline product was filtered and crystallized from CHCl$_3$/diethyl ether to afford 0.583 g (40%) of **60**, mp 144–150 °C; $[\alpha]^{25}_D$ = −2.8 ± 2.0° (*c* = 1.04, ethanol); ^{1}H NMR 300 MHz (CDCl$_3$) δ 2.03 (s, 3, C*H*$_3$CONH), 2.39 (s, 3, C*H*$_3$Ar), 2.68 (s, 3, C*H*$_3$SO), 3.78 (m, 2, C*H*$_2$NHAc), 3.84 (dd, *J* = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.071 (dd, *J* = 8, 8 Hz, 1, C-4 *H* cis to C-5 *H*, one sulfoxide diastereomer), 4.073 (dd, *J* = 8, 8 Hz, 1, C-4 *H* cis to C-5 H, other sulfoxide diastereomer), 4.78 (m, 1, C-5 *H*), 6.34 (t, 1, *J* = 6 Hz, *H*NCOCH$_3$), and 7.51 and 7.93 (AB, J_{AB} = 7 Hz, 2, aromatic C-6' and C-5' *H*, respectively), and 7.48 (s, 1, C-2' *H*); IR (KBr) 3290, 1755, 1652, and 1600 cm^{-1}; UV (EtOH) λ_{max} (log ε) 259 (4.08) nm. Anal. ($C_{14}H_{18}N_2O_4S$) C, H, N, S.

(*S*)-*N*-[[3-[3-Nitro-4-(methylsulfinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (61). Using the procedure described for preparation of **60**, 1.36 g (4 mmol) of **57** afforded 1.232 g (87%) of **61**, mp 180–181 °C (from CH$_3$OH); $[\alpha]^{25}_D$ = −34.2 ± 0.8° (*c* = 0.94, CH$_3$OH); ^{1}H NMR 360 MHz (DMSO-d_6) δ 1.83 (s, 3, C*H*$_3$CONH), 2.86 (s, 3, C*H*$_3$SO), 3.46 (dd, *J* = *J'* = 6 Hz, 2, C*H*$_2$NHAc), 3.88 (m, 1, C-4 *H* trans to C-5 *H*), 4.48 (dd, *J* = 8, 8 Hz, 1, C-4 *H* cis to C-5 *H*, one sulfoxide diastereomer), 4.52 (dd, *J* = 8, 8 Hz, 1, C-4 *H* cis to C-5 *H*, other sulfoxide diastereomer), 4.82 (m, 1, C-5 *H*), 8.05 and 8.17 (AB, J_{AB} = 7 Hz, 2, aromatic C-6' and C-5' H, respectively), 8.25 (s, 1, C-2' H), and 8.68 (t, *J* = 5 Hz, 1, *H*NCOCH$_3$); IR (KBr) 3420, 1750, 1655, 1535, and 1345 cm^{-1}; UV (EtOH) λ_{max} (log ε) 347 (3.32) and 251 (4.40) nm. Anal. ($C_{13}H_{15}N_3O_6S$) C, H, N, S.

(*S*)-*N*-[[3-[3-(Methylsulfonyl)-4-acetylphenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (62). To a solution of 2.40 g (7.4 mmol) of **54** in 150 mL of CHCl$_3$ at 0–5 °C was added 3.2 g (15 mmol) of 85% *m*-chloroperbenzoic acid in small portions. The mixture was allowed to warm to ambient temperature and then stirred for 18 h. The mixture was then heated under reflux for 4.5 h to bring product formation to completion. The solvent was removed in vacuo, and the residue was triturated with diethyl ether, which produced a gel. The gel was filtered and freed of trapped solvent by pumping to leave 1.4 g of **62**: mp 92–93 °C; $[\alpha]^{25}_D$ = −41.3 ± 0.4° (*c* = 2.02, water); ^{1}H NMR 360 MHz (CDCl$_3$) δ 2.03 (s, 3, C*H*$_3$CONH), 2.63 (s, 3, C*H*$_3$CO), 3.33 (s, 3, C*H*$_3$S), 3.68 (m, 2, C*H*$_2$NHAc), 3.90 (dd, *J* = 9, 7 Hz, 1, C-4 *H* trans to C-5 *H*), 4.17 (dd, *J* = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.86 (m, 1, C-5 *H*), 6.39 (m, 1, *H*NCOCH$_3$), and 7.54, 8.00, and 8.09 (ABC, J_{AB} = 8 Hz, J_{BC} = 2 Hz, 3, C-6', C-5', and C-2' *H*'s, respectively). Anal. ($C_{15}H_{18}N_2O_6S$) C, H, N, S.

(*S*)-*N*-[[3-(2,3-Dihydro-1-oxo-1*H*-inden-5-yl)-2-oxo-5-oxazolidinyl]methyl]acetamide (63). To a solution of 3.58 g of chromium(VI) oxide in 35 mL of acetic acid and 8.75 mL of water at ambient temperature was added in portions a solution of 7.0 g (25.5 mmol) of **8** in 35 mL of acetic acid and 10.6 mL of acetic anhydride, and the mixture was stirred for 18 h at ambient temperature. Then the mixture was extracted three times with CH_2Cl_2, and the combined organic solutions were washed with saturated NaHCO$_3$ and brine, dried (MgSO$_4$), and evaporated in vacuo to afford the crude product, which was purified by flash column chromatography to yield 2.55 g (35%) of **63**: mp 163–165 °C; $[\alpha]^{25}_D$ = −44° (*c* = 1, CH$_3$CN); HRMS (HPLC purity 95.8%); ^{1}H NMR 200 MHz (CDCl$_3$) δ 2.03 (s, 3, C*H*$_3$CONH), 2.70 (t, 2, C*H*$_2$CH$_2$C=O), 3.13 (t, 2, CH$_2$C*H*$_2$C=O), 3.70 (t, *J* = 5 Hz, 2, C*H*$_2$NHAc), 3.88 (dd, *J* = 8, 5.5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.13 (dd, *J* = 8, 7 Hz, 1, C-4 *H* cis to C-5 *H*), 4.83 (m, 1, C-5 *H*), 6.43 (m, 1, *H*NCOCH$_3$) 7.50 and 7.73 (AB, C-5' and C-6' *H*), and 7.67 (s, 1, aromatic C-2' *H*); IR (CHCl$_3$) 1759, 1699, and 1608 cm^{-1}.

B. In Vitro Susceptibility Tests. MIC's of the compounds for the various bacterial strains were determined by a microtiter broth dilution assay.[8,9] For comparative purposes, MIC's of racemic compounds were divided by two to reflect the fact that only one oxazolidinone enantiomer possesses antibacterial activity.

Registry No. **3**, 139071-68-4; **3** isocyanato, 33484-67-2; **4**, 139071-69-5; **4** isocyanato, 59741-17-2; **5**, 139071-70-8; **5** isocyanato, 139072-17-6; **6**, 139071-71-9; **6** isocyanato, 139072-18-7; **7**, 139071-72-0; **7** isocyanato, 139072-19-8; **8**, 120912-42-7; **8** isocyanato, 120912-37-0; **9**, 139071-73-1; **9** isocyanato, 139072-20-1; **10**, 139071-74-2; **10** isocyanato, 2243-54-1; **11**, 139071-75-3; **11** isocyanato, 54132-75-1; **12**, 139071-76-4; **12** isocyanato, 54132-76-2; **13**, 139071-77-5; **13** isocyanato, 51163-27-0; **14**, 104421-21-8; **15**, 96800-17-8; **16**, 96800-41-8; **17**, 96800-15-6; **18**, 114992-51-7; **19**, 115006-55-8; **20**, 139071-78-6; **21**, 96799-96-1; **21** 3-(4-nitrophenyl), 96799-95-0; **22**, 139071-79-7; **23**, 139071-80-0; **24**, 139071-81-1; **25**, 139071-82-2; **27**, 139071-83-3; **28**, 139071-84-4; **29**, 139071-85-5; **30**, 139071-86-6; **31**, 139071-87-7; **32**, 139071-88-8; **33**, 139071-89-9; **34**, 139071-90-2; **35**, 139071-91-3; **35** (X = F), 139072-21-2; **36**, 139071-92-4; **36** (X = F), 139072-22-3; **37**, 139071-93-5; **38**, 139071-94-6; **39**, 139071-95-7; **40**, 139071-96-8; **41**, 139071-97-9; **42**, 139071-99-1; **43**, 139071-99-1; **44**, 139072-00-7; **45**, 139072-01-8; **46**, 139072-02-9; **47**, 139072-03-0; **48**, 139072-04-1; **49**, 139072-05-2; **50**, 139072-06-3; **51**, 114992-76-6; **52**, 114992-77-7; **53**, 139072-07-4; **54**, 139072-08-5; **55**, 139072-09-6; **56**, 139072-10-9; **57**, 139072-11-0; **57**, 139072-25-6; **57**, 139072-26-7; **57**, 139072-27-8; **58**, 139072-12-1; **59**, 139072-13-2; **60**, 139072-14-3; **61**, 139072-15-4; **62**, 139072-16-5; **63**, 120912-43-8; $PdCl_2(PPh_3)_2$, 13965-03-2; trimethylsilylacetylene, 1066-54-2; (*S*)-*N*-[[3-[4-[(trimethylsilyl)ethynyl]-3-(trifluoroacetamido)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 139072-23-4; (*S*)-*N*-[[3-[4-ethynyl-3-(trifluoroacetamido)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 139072-24-5.

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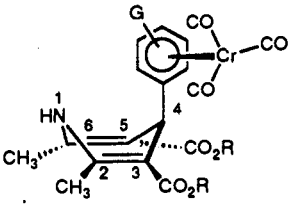
Communications to the Editor

Tricarbonylchromium Complexes of Hantzsch Esters Possess Robust Calcium Antagonist Activity†

4-Aryl-1,4-dihydropyridines (Hantzsch esters) are important cardiovascular drugs which exhibit calcium channel antagonist activity.[1] Interest in the synthesis of this class of compounds continues, both to elucidate the molecular basis of action and to improve their pharmacological profile.[2] (Arene)chromium tricarbonyl derivatives have found wide application in synthesis[3] and, more recently, in biological applications[4] as probes of drug–receptor binding. A central question for the potential use of a functionalized drug as a probe of any drug–receptor interaction is whether the structural change introduced perturbs the binding or abolishes biological activity.[5] We herein report the first preparation of tricarbonylchromium 4-aryl-1,4-dihydropyridines,[6] and present evidence that these molecules are robust and stable calcium antagonists which compete with [^{3}H]-1,4-dihydropyridine binding at Ca^{2+} channels in cardiac membranes.



Results and Discussion

Dihydropyridine complexes of chromium are known wherein the η^6 tricarbonylchromium (TCC) is bound to the dienamine function.[6a–e] Recently, TCC–dihydropyridine complexes have been obtained by nucleophilic addition to TCC–pyridine complexes.[6f] We present here compounds which, to the best of our knowledge, represent the first examples of metalation selectively on the 4-aryl ring in the presence of a 1,4-dihydropyridine. Regioselectivity was clearly established as η^6 to the 4-aryl substituent by the

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