Antibacterials. Synthesis and Structure–Activity Studies of 3-Aryl-2-oxooxazolidines. 2. The "A" Group

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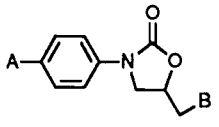
The synthesis and structure–activity relationship (SAR) studies of the effect of varying the "A" group in a series of 5-(acetamidomethyl)oxazolidinone antibacterials (2) are described. Compounds 2 were principally prepared either by the six-step synthesis described previously (*J. Med. Chem.* **1989**, *32*, 1673.) or by elaboration of the synthetic intermediate 2 (A = H) via electrophilic aromatic substitution or elaboration of the intermediate 2 (A = I) by transition metal catalyzed carbon–carbon bond-forming reactions. Antibacterial evaluation of compounds 2 with A = alkyl, ethenyl, ethynyl, hydroxyalkyl, aldo and keto, oximinoalkyl, carboalkoxy, nitro, amino, halo and ψ-halo, alkylthio, alkylsulfinyl, and alkylsulfonyl against *Staphylococcus aureus* and *Enterococcus faecalis* led to the identification of several SAR trends. In several series of homologues (alkyl, keto, oximinoalkyl, amino, halo and ψ-halo, and alkylthio), antibacterial activity increased with increasing lipophilicity. But in series with where A is a substituent with a tri- or tetrasubstituted (substituent larger than H) quaternary atom attached directly to the aromatic ring (hydroxyalkyl, alkylsulfinyl, alkylsulfonyl), the activity peaked at the member of the series with the "*tert*-butyl" connectivity pattern. Conjugated electron-withdrawing substituents also had increased activity relative to nonconjugated analogues of comparable lipophilicity.

The oxazolidinones are a new class of orally active, synthetic antibacterial agents. In the first paper of this series[1] we described the synthesis and systematically examined the structure–activity relationships of several different unrelated series of "A" functional group analogues bearing different "B" substituents (1). We concluded that,



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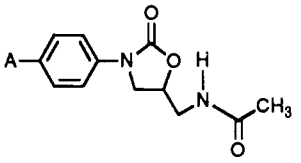

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except for the very hydrophilic sulfonamide "A" substituent, in each "A" group series the entry bearing the acetamide "B" group appeared to be the most active. Having established the superiority of the acetamide as a "B" group pharmacophore, we will now examine the effect on antibacterial activity of systematically varying the "A" group in the 4-position of the aromatic ring in several homologous or related series of (acetamidomethyl)oxazolidinones (2).

Chemistry

A six-step synthesis (Scheme I) of 5-(acetamidomethyl)oxazolidinones has been described previously.[1] The properties of compounds in this study which have been prepared by this route are summarized in Table I.

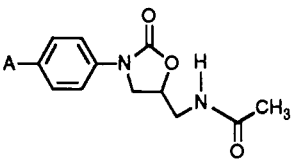
The remaining compounds described in this study were prepared principally by application of electrophilic aromatic substitution chemistry to the parent phenyl compound 21.[1]

Iodination of 21 afforded 4-iodo compound 22, which served as a key intermediate for incorporating many functional groups (Scheme II). Heck reaction of 22 with (trimethylsilyl)acetylene led to 23, whose silyl group was cleaved to yield (ethynylphenyl)oxazolidinone 24. Reduction of 24 with hydrogen using Lindlar catalyst afforded styrene 25. Application of transition metal catalyzed carbonylation technology to 22 yielded aldehyde 26 and ester 27. A crossed Ullmann reaction between 22 and pentafluoroethyl iodide afforded 28.

Functionalization of tolyl compound 3 was used to prepare 29 and 30 (Scheme III).

Acetyl compound 31[1] served as a versatile intermediate to targeted alkanol analogues (Scheme IV). Hydrolysis of 31 to 32 and conversion of the amino group to disilazole derivative 33 allowed selective Grignard addition to the keto group to afford 34, which was deprotected and acetylated to give the desired tertiary alcohol 35. Reduction of 31 and homologous ketones 36–38 (prepared by Friedel–Crafts acylation of 21) was used to prepare the corresponding alcohols 39–42.

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



no.	A	mp, °C	formula	anal.
3	CH_3	141–142	$C_{13}H_{16}N_2O_3$	C, H, N
4	C_2H_5	135–136	$C_{14}H_{18}N_2O_3$	C, H, N
5	n-C_3H_7	111.5–112.5	$C_{15}H_{20}N_2O_3$	C, H, N
6	n-C_4H_9	120–121	$C_{16}H_{22}N_2O_3$	C, H, N
7	t-C_4H_9	145.5–146.5	$C_{16}H_{22}N_2O_3$	C, H, N
8	$C_2H_5O_2C$	150–151	$C_{15}H_{18}N_2O_5$	C, H, N
9	O_2N	194.5–195.5	$C_{12}H_{13}N_3O_5$	C, H, N
10	CH_3O	149–149.5	$C_{13}H_{16}N_2O_4$	C, H, N
11	n-C_4H_9O	137–138.5	$C_{16}H_{22}N_2O_4$	C, H, N
12	C_6H_5O	135–135.5	$C_{18}H_{18}N_2O_4$	C, H, N
13	F	135–136	$C_{12}H_{13}FN_2O_3$	C, H, N, F
14	Cl	155–156	$C_{12}H_{13}ClN_2O_3$	C, H, N, Cl
15	Br	180–182	$C_{12}H_{13}BrN_2O_3$	C, H, N, Br
16	NC	153–154	$C_{13}H_{13}N_3O_3$	C, H, N
17	CF_3	183–184	$C_{13}H_{13}F_3N_2O_3$	C, H, N
18	C_2H_5S	148.5–149.5	$C_{14}H_{18}N_2O_3S$	C, H, N, S
19	C_3H_7S	141.5–142	$C_{15}H_{20}N_2O_3S$	C, H, N, S
20	C_6H_5S	123–124	$C_{18}H_{18}N_2O_3S$	C, H, N, S

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‡ Chemotherapy Research, Glenolden Laboratory.

(1) Gregory, W. A.; Brittelli, D. R.; Wang, C.-L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Bartholomew, P. T.; Slee, A. M.; and Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673.

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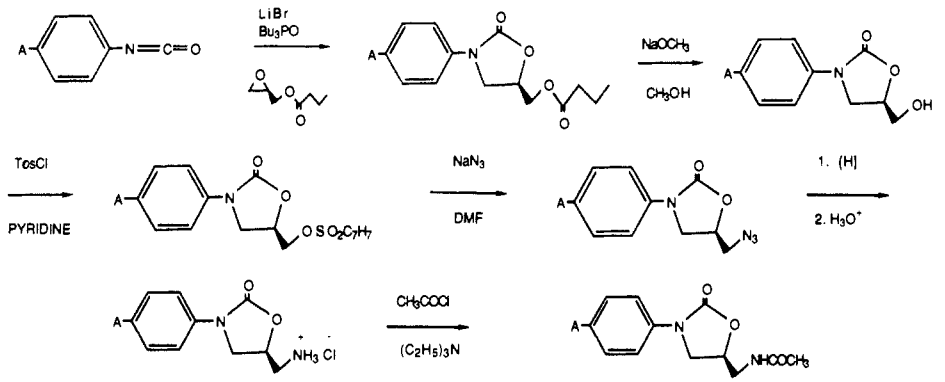
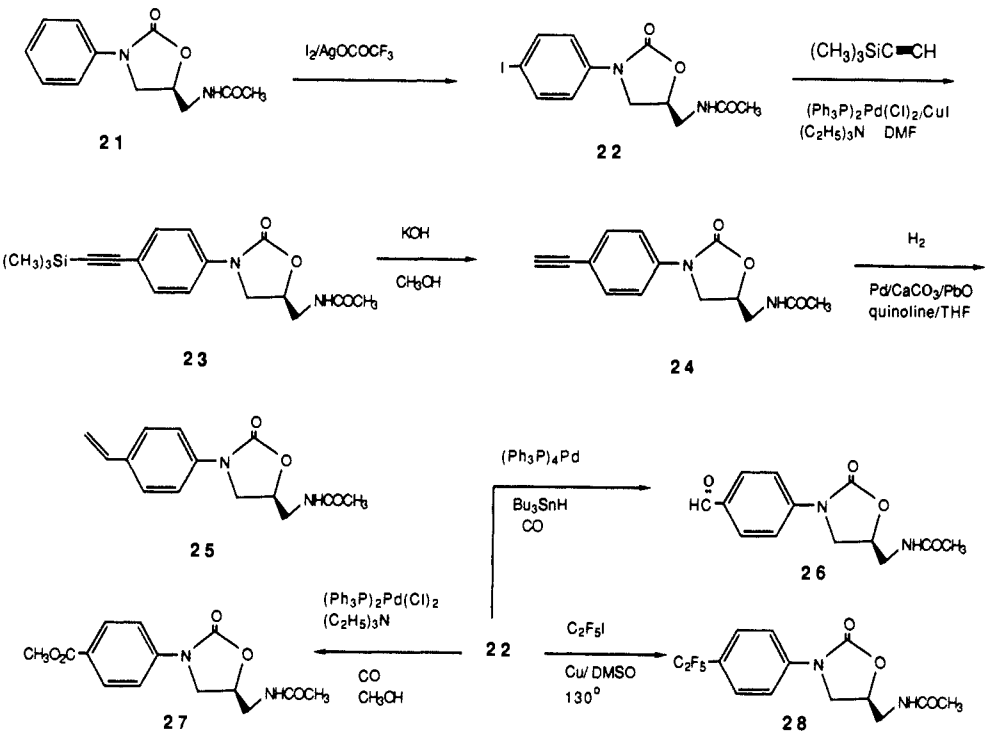
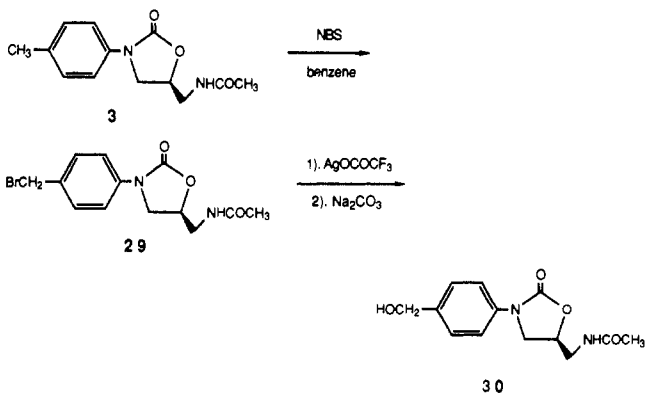
Scheme I



Scheme II



Scheme III



Oxazolidinones bearing substituted acetyl "A" groups were prepared by using two different strategies (Scheme V). The parent **21** was chloroacetylated to yield **43**, which was converted to the acetate **44**. A variety of other substituted acetyl derivatives were synthesized via bromo intermediates derived from ketone bromination. Bromination of **31** led to **45**. Similarly, the acetyl-substituted butyrate was converted to its bromide, from which crown ether assisted fluoride displacement and the final five steps of the synthesis in Scheme I gave **46**. Analogously, bromination of the azidomethyl methyl ketone followed by displacement by sodium azide gave the bis azide, whose reduction and acetylation afforded **47**.

Cyanoacetyl compound **48** was prepared by condensation of **31** with DMF acetal followed by heterocyclization and base-catalyzed isoxazole degradation (Scheme VI).

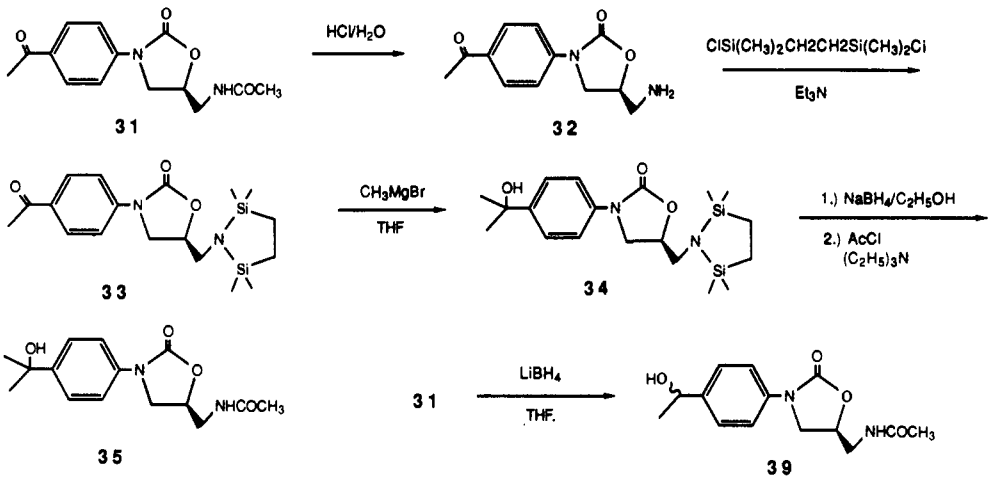
Dialkylamino-substituted compounds were obtained by a modification of the principal synthesis outlined in Scheme I (Scheme VII). This was necessitated by the incompatibility of isocyanate and tertiary amino groups.[2] Conversion of (dialkylamino)benzoic acids to acyl azides proceeded smoothly. Simultaneous addition of these azides and glycidyl azide[3] to refluxing xylene containing the hydrocarbon-soluble cycloaddition catalyst[4] led to nitrogen loss and formation of the oxazolidinone azide, presumably by Curtius rearrangement of the nitrene to the

(2) Tertiary amines are known to catalyze dimerization and trimerization of isocyanates, hence monomeric amino-containing isocyanates are unknown. W. Schafer In *Methoden der Organischen Chemie*; Houben, J., Weyl, T., Eds.; G. Theime: Stuttgart, 1983; Vol. E4, 1104.

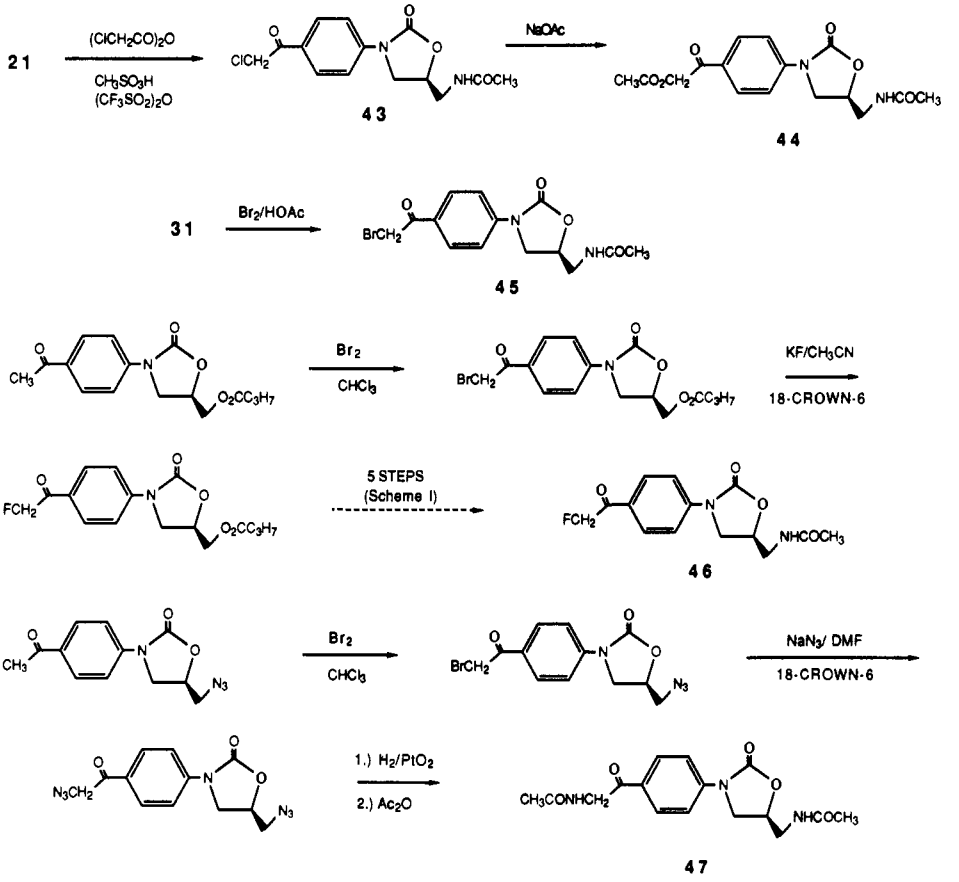
(3) Ingham, J. D.; Petty, W. L.; Nichols, R. L., Jr. *J. Org. Chem.* **1956**, *21*, 373.

(4) Herweh, J. E.; Kauffmann, W. J. *Tetrahedron Lett.* **1971**, 809.

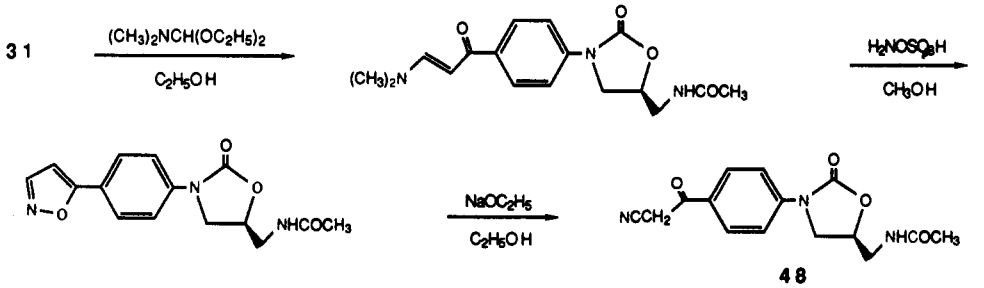
Scheme IV



Scheme V



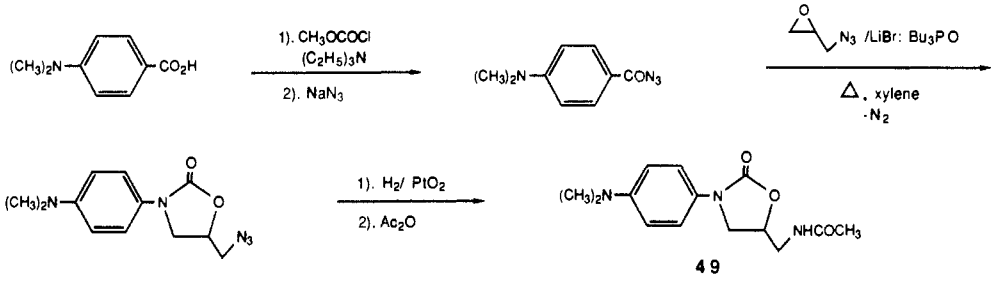
Scheme VI



isocyanate and subsequent conventional reaction of the latter with the epoxide. Reduction and acetylation of the azide afforded **49**. The diethylamino analogue **50** was prepared by the same route.

An investigation into the effect of the absolute configuration of the methyl sulfoxide group on antibacterial activity was made possible by applying Kagan's asymmetric oxidizing methodology[5] to **51** (Scheme VIII), re-

Scheme VII



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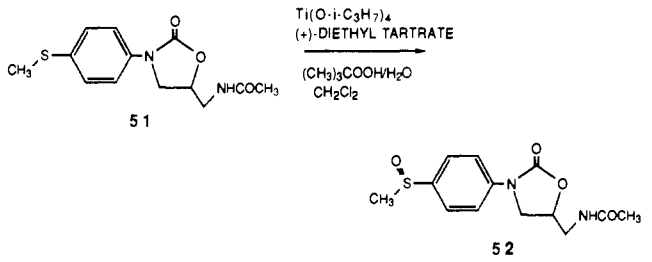
Scheme VIII



51 52

sulting in formation of the *R,S* product **52** as formulated and the *S,S* diastereomer **53** when (−)-diethyl tartrate was used as the chiral titanium ligand.

Compounds bearing fluoro-containing thiomethyl substituents were prepared via reactions outlined in Scheme IX. Sulfoxide **72** was converted to monofluoro sulfide **54** by a DAST-induced Pummerer rearrangement. Reduction of chlorosulfonyl compound **55** to **56** and alkylation of **56** under electron-transfer conditions afforded trifluoromethyl sulfide **57**.

Sulfoxides **58–61** and sulfones **62–65** were prepared by oxidation of the corresponding sulfides under appropriate conditions.

Acetonyl ketone **66** was prepared by copper-mediated reaction of **22** with the potassium salt of 2,4-pentanedione as described for **28**. Oximes **67–69** were prepared from the respective ketones by prosaic methods. Amine **70** was prepared by catalytic reduction of nitro compound **9**. The synthesis of compounds **71–73** has been described previously.[1]

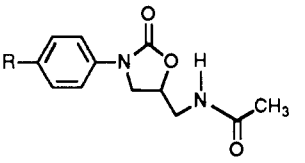
Structure–Activity Relationships

The in vitro antimicrobial activities of a series of alkyl "A" group oxazolidinone acetamide homologues are summarized in Table II. Activity increases dramatically with increasing aliphatic carbon content, leveling off at about the three-to-four carbon substituent size, suggesting that at this point a required threshold lipophilicity has been achieved. In terms of the hydrophobic parameter log *P*, which quantifies lipophilicity as a log of the partition coefficient of a particular solute distributed between octanol and water, this threshold corresponds to a calculated log *P* of between 1.5 (for A = ethyl) and 2.0 (for A = propyl). A similar decrease in activity with decreasing lipophilicity is apparent among the increasingly unsaturated two-carbon series of **4**, alkene **25**, and alkyne **24**. One other apparent effect is the advantage that accrues to the shape of the compact *t*-Bu substituent in **7**. Both these themes recur in subsequent SAR vignettes in this study. For instance, among the carbonyl homologues of Table III, the effect of increasing lipophilicity is again evident in going from aldehyde **26** to butyryl ketone **37**.

Another striking effect is the difference in activity between equally lipophilic acetonyl compound **66** and its conjugated isomer **36**. This difference could be rationalized as an indication that conjugation between electron-withdrawing substituents and the oxazolidinone nitrogen plays an important role in enhancing in vitro antibacterial activity.

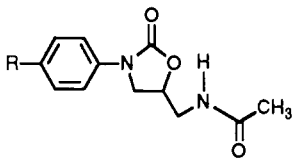
The activity of the substituent acetyl analogues (**44–48**) presents no conclusive trends. The acetoxy, fluoro, and

Table II. Antibacterial Activities of Oxazolidinones with Aliphatic "A" Groups



no.	R	C-5 config	MIC, μg/mL *S. aureus* SFCO-1a	MIC, μg/mL *E. faecalis* STCO-19
21	H	*S*	128	128
3	CH_3	*S*	32	32
4	C_2H_5	*S*	4	8
5	$n\text{-}C_3H_7$	*S*	2	4
71	$i\text{-}C_3H_7$	*R,S*	4	4
6	$n\text{-}C_4H_9$	*R,S*	4	4
7	$(CH_3)_3C$	*S*	1	2
25	$CH_2{=}CH$	*S*	4	8
24	HC≡C	*S*	16	16

Table III. Antibacterial Activities of Oxazolidinones with Carbonyl "A" Groups



no.	R	C-5 config	MIC, μg/mL *S. aureus* SFCO-1a	MIC, μg/mL *E. faecalis* STCO-19
26	H(C=O)	*S*	8	8
31	CH_3(C=O)	*S*	0.5	1
36	C_2H_5(C=O)	*S*	1	0.5
66	CH_3(C=O)(CH_2)	*S*	4	8
37	$n\text{-}C_3H_7$(C=O)	*S*	0.25	0.25
38	$(CH_3)_2CH$(C=O)	*S*	1	1
46	FCH_2(C=O)	*S*	2	2
43	$ClCH_2$(C=O)	*S*	0.5	2
45	$BrCH_2$(C=O)	*S*	4	8
48	$NCCH_2$(C=O)	*S*	8	64
47	$CH_3CONHCH_2$(C=O)	*S*	8	16
44	CH_3(C=O)OCH_2(C=O)	*S*	0.5	2
27	CH_3O(C=O)	*S*	2	2
8	C_2H_5O(C=O)	*R,S*	4	4

(5) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.

Scheme IX

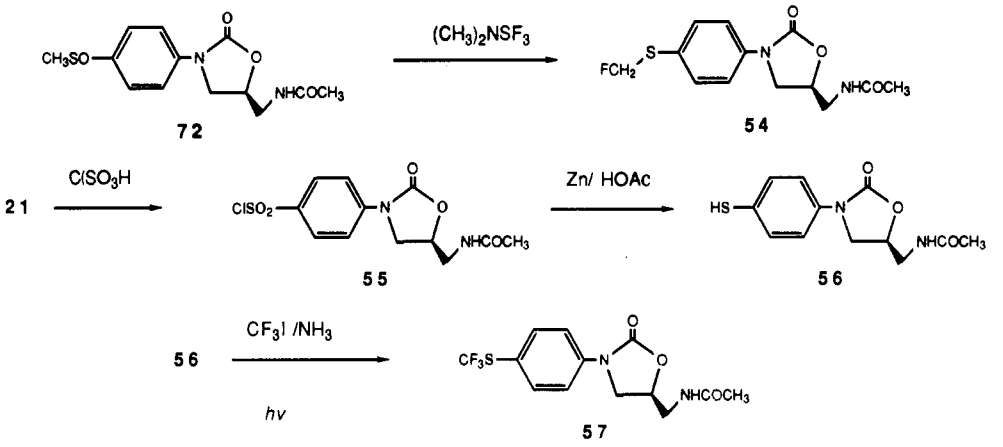
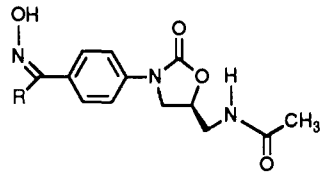


Table IV. Antibacterial Activities of Oxazolidinones with Oxime "A" Groups



no.	R	MIC, μg/mL *S. aureus* SFCO-1a	MIC, μg/mL *E. fecalis* STCO-19
67	H	16	16
68	CH_3	4	2
69	n-C_3H_7	4	4

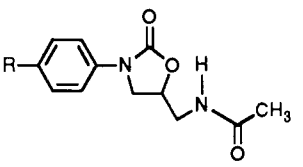
chloro substituents are innocuous; cyano, acetamido, and bromo substituents reduce activity compared to the unsubstituted acetyl compound **31**. Esters **27** and **8**, which are formally related to ketones **31** and **36** by insertion of an oxygen atom, are also less active than the latter. Conversion of ketones to the corresponding oximes also results in a reduction in antibacterial activity (Table IV). We suggest that the reduced activity in all these cases is related to the lowered lipophilicities of these compounds relative to **31**.

The secondary alcohols in Table V are all substantially less active than their ketone counterparts, which provides additional evidence for the role of conjugation. The two α-methyl branched alcohols **39** and **35** are more active than their higher homologues **41** and **42**, the increased lipophilicity of the latter notwithstanding, an observation we would again suggest reflects some advantage accruing to compact tetrahedral functional groups as mentioned earlier in the context of the isomeric butyl analogues.

A familiar pattern emerges for the nitrogen functional groups of Table VI. Nitro compound **9** has good antibacterial activity, in common with other 3-phenyloxazolidinones bearing electron-withdrawing substituents. While the corresponding amine **70** was inactive, alkylated derivatives of **70** had modest activities. Ethers **10** and **11** present a similar picture. We would rationalize both these sets of data as reflecting increased activity with increases in lipophilicity. The poor activity of phenyl ether **12** is a noteworthy contradiction to this trend.

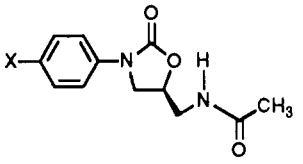
The activities of the halo and ψ-halo derivatives presented in Table VI are strictly in keeping with their relative lipophilicities. In this respect, the activities of the fluorocarbon-substituted compounds **17** and **28** go hand in hand with their lipophilicities relative to the corresponding hydrocarbon substituted compounds **3** and **4**. We would

Table V. Antibacterial Activities of Oxazolidinones with Hydroxyalkyl "A" Groups



no.	R	C-5 config	MIC, μg/mL *S. aureus* SFCO-1a	MIC, μg/mL *E. faecalis* STCO-19
30	$HOCH_2$	*R,S*	32	16
39	$CH_3CH{\sim}OH$	*S*	4	4
40	$C_2H_5CH{\sim}OH$	*S*	32	64
35	$(CH_3)_2C{\sim}OH$	*S*	2	4
41	n-$C_3H_7CH{\sim}OH$	*S*	16	32
42	$(CH_3)_2CHCH{\sim}OH$	*S*	4	8

Table VI. Antibacterial Activities of Oxazolidinones with Nitro, Amino, Ether, Halo, and ψ-Halo "A" Groups

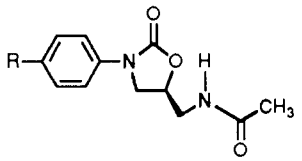


no.	X	C-5 config	MIC, μg/mL *S. aureus* SFCO-1a	MIC, μg/mL *E. faecalis* STCO-19
9	O_2N	*S*	2	2
70	H_2N	*S*	128	128
49	$(CH_3)_2N$	*S*	16	16
50	$(C_2H_5)_2N$	*S*	8	16
10	CH_3O	*R,S*	32	32
11	n-C_4H_9O	*S*	8	16
12	C_6H_5O	*R,S*	64	64
13	F	*R,S*	>64	>64
14	Cl	*R,S*	32	64
15	Br	*S*	16	8
22	I	*S*	8	8
16	NC	*R,S*	16	16
17	CF_3	*S*	8	8
28	C_2F_5	*S*	2	2

suggest that the better than expected (for such a hydrophilic group) activity of the cyano compound **16** could reflect its electron-withdrawing properties.

The activities of the sulfur functional groups presented in Table VII are consistent with the qualitative SAR notions we have been advancing in this discussion. Thus, the methyl-substituted sulfides, sulfoxides, and sulfones have

Table VII. Antibacterial Activities of Oxazolidinones with Sulfur-Containing "A" Groups



no.	R	MIC, μg/mL *S. aureus* SFCO-1a	MIC, μg/mL *E. faecalis* STCO-19
51	CH_3S	4	4
18	C_2H_5S	1	2
19	n-C_3H_7S	8	8
20	C_6H_5S	>128	128
72	CH_3SO	4	4
58	C_2H_5SO	16	16
59	n-C_3H_7SO	32	64
52	(R)-CH_3SO	4	4
53	(S)-CH_3SO	8	16
73	CH_3SO_2	4	4
62	$C_2H_5SO_2$	8	8
63	n-$C_3H_7SO_2$	32	32
57	CF_3S	4	4
60	FCH_2SO	8	8
61	CF_3SO	2	2
64	FCH_2SO_2	1	1
65	CF_3SO_2	2	2

comparable activity. Note that the methyl sulfone has the same connectivity as a t-Bu group. The antibacterial activity of longer chain-length sulfoxides and sulfones drops off, just as had been observed with the corresponding isoatomic alcohols. Aryl sulfide **20** has extremely weak activity just like its chalogen analogue, ether **12**. With the stronger electron-withdrawing (trifluoromethyl) groups in **61** and **62**, increased activity is seen relative to the hydrocarbon analogues. A preference for the absolute configuration of the stereoisomeric sulfoxides **52** and **53** is seen, with R,S-sulfoxide **52** being more active than the S,S diastereomer. Curiously, **52** is remarkably water-soluble, having a solubility of 782 mg/mL, while the solubility of **53** is only 112 mg/mL (the solubility of racemate **72** is 311 mg/mL).

Summary

Several themes recur in these structure–activity studies of "A" groups in the 4′-position of 3-phenyloxazolidinones. In several series, antibacterial activity increases with increasing lipophilicity of the substituents in an homologous series (alkanes, alkyl ketones, halogens). Several close comparisons also show that conjugated, strongly electron-withdrawing substituents confer enhanced activity on oxazolidinones relative to corresponding closely-related electron-donating substituents of comparable lipopholicity (nitro vs amino, ketones vs alcohols), and series of substituents with tetrahedral carbon or sulfur atoms bearing at least two other non-hydrogen substituents possess maximum activity with methyl substituents and suffer lowered activity with increasing chain length (alcohols, sulfoxides, sulfones). This latter observation suggests that a group at this position must be compact if it is not relatively flat.

Experimental Section

Chemistry. Melting points were determined on Thomas-Hoover and Meltemp capillary and Büchi 510 automatic melting point apparatus and are uncorrected. Infrared spectra were recorded with KBr disks and Perkin-Elmer Model 21 and 137 spectrophotometers and are reported in reciprocal centimeters. ^{1}H NMR spectra were determined in the indicated solvent on Varian A-60, Varian T-60, Varian EM-390, IBM NR200-SY, 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 a Finnigan MAT Model 8230 mass spectrometer. Ultraviolet spectra were taken in absolute ethanol with a Cary 21 spectrophotometer.

5-(Acetamidomethyl)oxazolidinones **3–20** 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 **21**, **31**, **51**, and **71–73** have been described.[1]

(*S*)-*N*-[[3-(4-Iodophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (22). To 23.4 g (0.10 mol) of **21** in 300 mL of $CHCl_3$ and 200 mL of acetonitrile was added 29.0 g (0.132 mol) of silver trifluoroacetate followed by 25.4 g (0.10 mol) of iodine, in small portions. Additional iodine was added until the mixture retained the purple iodine color (~1.6 g was required). The mixture was stirred for 18 h and then filtered and the solvent was removed in vacuo. The resulting residue was triturated with water, and the solid was filtered, washed with water, very dilute ammonium hydroxide, and water, and vacuum dried. The product was crystallized from acetonitrile to yield 23.090 g of **22** (64%), mp 195.5–197 °C. A second crop of 1.672 g was obtained: ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.83 (s, 3, CH_3CONH), 3.42 (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), 4.73 (m, 1, C-5 H), 7.40 and 7.64 (AB, J_{AB} = 8.0 Hz, 4, C-3′ and C-5′ H's and C-2′ and C-6′ H's, respectively), and 8.27 (m, 1, HNCOCH$_3$). Anal. ($C_{12}H_{13}N_2O_3I$) C, H, N.

(*S*)-*N*-[[3-[4-[2-(Trimethylsilyl)ethynyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (23). To 5.0 g (13.8 mmol) of **22** and 1.62 g (16.5 mmol) of (trimethylsilyl)acetylene in 20 mL of DMF and 20 mL of triethylamine was added 0.193 g (2 mol %) of bis(triphenylphosphine)palladium(II) chloride and 0.026 g (1 mol %) of copper(I) iodide, and the mixture was stirred for 4.5 h at 45 °C. The solvent was then removed in vacuo and the resulting residue was dissolved in acetonitrile and ether and washed with water. The solvent was removed in vacuo and the residue was chromatographed on silica gel eluting with 1:1 1,2-dimethoxyethane (glyme)/cyclohexane to yield 3.4 g (84%) of **23**: mp 143–145 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.23 (s, 9, $(CH_3)_3$Si), 1.83 (s, 3, CH_3CONH), 3.42 (t, J = 5 Hz, 2, CH_2NHAc), 3.77 (dd, J = 8, 5 Hz, 1, C-4 H trans to C-5 H), 4.13 (dd, J = 7, 7 Hz, 1, C-4 H cis to C-5 H), 4.73 (m, 1, C-5 H), 7.48 and 7.57 (AB, J_{AB} = 9 Hz, 4, C-3′ and C-5′ H's and C-2′ and C-6′ H's, respectively), and 8.27 (m, 1, HNCOCH$_3$).

(*S*)-*N*-[[3-(4-Ethynylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (24). To 2.0 g (6.1 mmol) of **23** in 50 mL of methanol was added 10 mL of 1 N aqueous potassium hydroxide and the solution was stirred for 90 min at 25 °C. The solution was then adjusted to pH 3 by adding dilute hydrochloric acid. The resulting solution was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated to dryness in vacuo. The resulting residue was chromatographed on silica gel with 1:1 glyme/cyclohexane, and the product fractions were combined and crystallized from CH_2Cl_2/n-hexane to yield 0.98 g (63%) of **24**: mp 169.5–171.5 °C; $[\alpha]^{25}_D$ = −32.2° ± 0.4° (c = 1.01, methanol); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.84 (s, 3, CH_3CONH), 3.42 (t, J = 5 Hz, 2, CH_2NHAc), 3.77 (dd, J = 8, 5 Hz, 1, C-4 H trans to C-5 H), 4.13 (dd, J = 7, 7 Hz, 1, C-4 H cis to C-5 H), 4.18 (s, 1, acetylenic H), 4.73 (m, 1, C-5 H), 7.43 and 7.57 (AB, J_{AB} = 9.5 Hz, 4, C-3′ and C-5′ H's and C-2′ and C-6′ H's, respectively), and 8.27 (m, 1, HNCOCH$_3$); ^{13}C NMR (67.1 MHz, DMSO-d_6) δ 22.402 (CH_3CONH), 41.344 and 47.004 (CH_2's), 71.625 (CH), 80.247 and 83.192 (acetylene), 116.291, 117.687, 132.380 and 138.820 (aromatic), 153.921 (oxazolidinone carbonyl), and 169.951 (acetamide carbonyl); IR (Nujol mull) 3380, 3280, 2100, 1740, 1660, 1605, and 1540 cm^{-1}. Anal. ($C_{14}H_{14}N_2O_3$) C, H, N.

(*S*)-*N*-[[3-(4-Ethenylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (25). A mixture of 1.33 g (5.15 mmol) of **24** and 2.00 g of 5% palladium on calcium carbonate (poisoned with lead(II) oxide) in 125 mL of THF and 5 mL of quinoline was placed under 1 atm of hydrogen and stirred at 25 °C for 2.5 h.

The mixture was then evaporated to dryness in vacuo. The resulting residue was chromatographed on silica gel with 1:1 glyme/cyclohexane to give a mixture of **25** and **4**. These compounds were separated by chromatography on 10% silver nitrate on silica gel with 9:1 chloroform/methanol to yield 0.450 g (34%) of **25**: mp 169–171 °C (polymerizes); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.83 (s, 3, CH_3CONH), 3.43 (t, J = 5 Hz, 2, CH_2NHAc), 3.77 (dd, J = 8, 5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.14 (dd, J = 7, 7 Hz, 1, C-4 *H* cis to C-5 *H*), 4.73 (m, 1, C-5 *H*), 5.19 (d, J = 12.2 Hz, 1, trans H_2C=CH), 5.75 (d, J = 19.0 Hz, 1, cis H_2C=CH), 6.73 (dd, J = 12.2 Hz, J' = 19.0 Hz, 1, CH_2=C*H*), 7.44 and 7.53 (AB, J_{AB} = 3.0 Hz, 4, C-3′ and C-5′ H's and C-2′ and C-6′ H's, respectively), and 8.25 (m, 1, *H*NCOCH$_3$); IR (Nujol mull) 3300, 3080, 1730, 1640, 1620, 1610, and 1560 cm^{-1}. Anal. ($C_{14}H_{16}N_2O_3$) C, H, N.

(*S*)-*N*-[[3-(4-Formylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (26). To 31.0 g (0.086 mol) of **22** and 10.0 g (0.0086 mol) of tetrakis(triphenylphosphine)palladium(0) in 400 mL of THF under carbon monoxide at 55 °C was added dropwise over the period of 6 h a solution of 44.0 g (0.136 mol) of tri-*n*-butyltin hydride in 65 mL of toluene. The mixture was allowed to cool to room temperature and then it was cooled to 0 °C, and the solid which crystallized was filtered and recrystallized from acetonitrile to yield 18.2 g (81%) of **26**: mp 172–173 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.87 (s, 3, CH_3CONH), 3.43 (t, J = 5 Hz, 2, CH_2NHAc), 3.82 (dd, J = 8, 5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.20 (dd, J = 7, 7 Hz, 1, C-4 *H* cis to C-5 *H*), 4.78 (m, 1, C-5 *H*), 7.77 and 7.95 (AB, J_{AB} = 7 Hz, 4, C-3′ and C-5′ H's and C-2′ and C-6′ H's, respectively) 8.28 (m, 1, *H*NCOCH$_3$), and 9.93 (s, 1, *CH*O). Anal. ($C_{13}H_{14}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Carbomethoxyphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (27). To 10.0 g (27.7 mmol) of **22** in 200 mL of methanol and 50 mL of triethylamine heated to boiling under carbon monoxide was added 2.50 g (3.57 mmol) of bis(triphenylphosphine)palladium(II) chloride. The mixture was heated under reflux and carbon monoxide for 6 h and then was allowed to cool to room temperature, diluted with CH_2Cl_2, and filtered through diatomaceous earth. The CH_2Cl_2 solution was washed with two 300-mL portions of 1 N aqueous ammonium chloride, dried (Na_2SO_4), and evaporated in vacuo. The resulting residue was dissolved in CH_2Cl_2 and the product was precipitated by the addition of hexane. The solid was filtered and crystallized from CH_2Cl_2/hexane to yield 1.0 g (12%): mp 179–181 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.83 (s, 3, CH_3CONH), 3.40 (t, J = 5.5 Hz, 2, CH_2NHAc), 3.80 (dd, J = 9, 6.5 Hz, 1, C-4 *H* trans to C-5 *H*), 3.83 (s, 3, CO_2CH_3), 4.17 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.76 (m, 1, C-5 *H*), 7.69 and 7.90 (AB, J_{AB} = 8.9 Hz, 4, C-3′ and C-5′ H's and C-2′ and C-6′ H's, respectively, and 8.25 (t, J = 5.8 Hz, 1, *H*NCOCH$_3$); ^{13}C NMR (67.1 MHz, DMSO-d_6) δ 22.33 (CH_3CONH), 41.30 and 47.06 (CH_2's), 51.85 (CO_2CH_3), 71.70 (*CH*), 117.19, 124.12, 130.12 and 142.55 (aromatic), 153.85 (oxazolidinone carbonyl), 165.68 (ester carbonyl), and 169.97 (acetamide carbonyl); IR (Nujol mull) 3307, 1737, 1708, 1658, 1621, and 1538 cm^{-1}. Anal. ($C_{14}H_{16}N_2O_5 \cdot H_2O$) C, H, N.

(*S*)-*N*-[[3-[4-(Pentafluoroethyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (28). A mixture of 3.0 g (8.3 mmol) of **22**, 6.5 g (25 mmol) of pentafluoroethyl iodide, and 0.6 g (9.35 mmol) of copper in 50 mL of DMSO was heated at 130 °C in a steel bomb for 28 h. The solvent was then removed in vacuo and the residue was chromatographed on silica gel with ethyl acetate to yield 0.800 g (27%) of **28**: mp 148–150 °C; $[\alpha]^{25}_D$ = −26° (*c* = 1.0, acetonitrile); mass spectrum ($C_{14}H_{13}N_2O_3F_5$) calcd *m/e* 352.0846, measured *m/e* 352.0857 (M$^+$).

(*S*)-*N*-[[3-[4-(Bromomethyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (29). To a warm solution of 2.5 g (10 mmol) of **3** and 1.8 g (10 mmol) of *N*-bromosuccinimide in 75 mL of benzene was added a few crystals of azobis(isobutyronitrile) and the mixture was heated under reflux for 90 min. The supernatant was decanted and evaporated to dryness in vacuo to give a solid, which was triturated with water, filtered, and air-dried. The crude product was crystallized from benzene/ethyl acetate to yield 0.56 g (17%): mp 160–161 °C; $[\alpha]^{25}_D$ = −27° (*c* = 1, acetone); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.03 (s, 3, CH_3CONH), 3.66 (m, 2, CH_2NHAc), 3.80 (dd, J = 9, 6.5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.07 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.50 (s, 2, CH_2Br), 4.78 (m, 1, C-5 *H*), 6.1 (t, J = 6 Hz, 1, *H*NCOCH$_3$), and 7.47 (q, 4, aromatic); IR (Nujol mull) 3300, 1740, 1720, and 1650 cm^{-1}.

(*S*)-*N*-[[3-[4-(Hydroxymethyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (30). To a solution of 0.9 g (4 mmol) of silver trifluoroacetate in 10 mL of anhydrous THF was added a warm solution of 1.3 g (4 mmol) of **29** in 15 mL of anhydrous THF. A precipitate formed immediately. The mixture was heated to boiling and filtered hot. The filtered solid was washed with anhydrous THF, and the combined filtrates were evaporated to dryness in vacuo. The resulting solid was redissolved in 10 mL of THF and the solution was treated with a saturated aqueous $NaHCO_3$ solution and stirred overnight. The mixture was then evaporated to dryness in vacuo and the residue was extracted with three portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were evaporated to dryness in vacuo, and the residue was chromatographed on silica gel with 1:3 hexane/THF to yield 0.035 g (3.3%) of **30**: mp 130–131 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.00 (s, 3, CH_3CONH), 3.67 (m, 2, CH_2NHAc), 3.78 (dd, J = 9, 6.5 Hz, 1, C-4 *H* trans to C-5 *H*), 4.07 (dd, J = 9, 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.67 (s, 2, CH_2OH), 4.76 (m, 1, C-5 *H*), 4.76 (m, 1, CH_2OH), 6.1 (br s, 1, *H*NCOCH$_3$), and 7.25 (q, 4, aromatic); mass spectrum ($C_{13}H_{16}N_2O_4$) calcd *m/e* 264.111, measured *m/e* 264.113 (M$^+$).

(*S*)-5-(Aminomethyl)-3-(4-acetylphenyl)-2-oxooxazolidine (32). A mixture of 12.0 g (0.043 mol) of **31**[1] and 100 mL of 1 N hydrochloric acid was heated under reflux for 3 h and then cooled and extracted twice with CH_2Cl_2 to remove unreacted **31**. The aqueous layer was treated with 100 mL of 1 N ammonium hydroxide and extracted twice with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was crystallized from 2-propanol to yield 8.4 g (84%) of **32**: mp 135–136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4 (br, 2, NH_2), 2.07 (s, 3, CH_3CO), 3.00 and 3.16 (d of AB, 2, CH_2NH_2), 3.95 (dd, J = 9, 6.5 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*), and 7.83 (q, 4, aromatic).

(*S*)-5-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-3-(4-acetylphenyl)-2-oxooxazolidine (33). To a solution of 3.5 g (15 mmol) of **32** and 3.5 g of triethylamine in 50 mL of CH_2Cl_2 under nitrogen was added dropwise a solution of 3.5 g (16.2 mmol) of 1,4-dichloro-1,1,4,4-tetramethyl-1,4-disilabutane in 6 mL of CH_2Cl_2, and the mixture was stirred for 2 h at ambient temperature. The solution was then washed successively with aqueous NaH_2PO_4 solution and water, dried ($MgSO_4$), and evaporated to dryness in vacuo to yield 3.8 g (67%) of **33** (mp 138–141 °C) pure enough to be used in the next reaction. A sample was crystallized from 2-propanol: mp 138–141 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.77 (br, 4, $SiCH_2CH_2Si$), 1.2 (s, 12, $SiCH_3$), 2.60 (s, 3, CH_3CO), 3.17 (ddd, 2, CH_2N), 3.80 (dd, J = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.03 (m, 1, C-4 *H* cis to C-5 *H*), 4.60 (m, 1, C-5 *H*), and 7.80 (q, 4, aromatic); IR (Nujol) 1742 and 1707 cm^{-1}. Anal. ($C_{18}H_{28}N_2O_3Si_2$) C, H, N.

(*S*)-5-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-3-[4-(1-hydroxy-1-methylethyl)phenyl]-2-oxooxazolidine (34). To a solution of 5.4 g (14 mmol) of **33** in 50 mL of anhydrous THF under nitrogen at 0 °C was added dropwise 8.0 mL (24 mmol) of a 3.0 M solution of methylmagnesium bromide in ether. The mixture was stirred at 0–5 °C for 30 min and at ambient temperature for 2.5 h and then poured into excess cold, saturated aqueous ammonium chloride solution. The mixture was extracted three times with CH_2Cl_2, the combined CH_2Cl_2 extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to yield 3.67 g (66%) of **34** as a light yellow, highly viscous liquid, which was used without further purification in the preparation of **35**.

(*S*)-*N*-[[3-[4-(1-Hydroxy-1-methylethyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (35). To a solution of 5.64 g (14 mmol) of **34** in 75 mL of ethanol was added in small portions 2.0 g of sodium borohydride and the resulting solution was heated under reflux for 6 h. The mixture was then evaporated to dryness in vacuo and the residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted twice with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to yield a semisolid, which was triturated with ether a few times. The foamy material (3.7 g) which was obtained after removal of the last traces of ether under reduced pressure was dissolved in 50 mL of THF and treated with 2.0 g of triethylamine and then dropwise with a solution of 1.4 g of acetyl chloride in 5 mL of THF. The mixture was stirred

at ambient temperature for 3 h and then evaporated to dryness in vacuo and the residue was treated with 20 mL of water and extracted three times with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to yield a sticky solid which was boiled with ethyl acetate and filtered to yield 0.72 g of a colorless material. The crude product was chromatographed on silica gel with THF to afford 0.30 g (7%) of 35: mp 178–180 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.40 (s, 6, $(CH_3)_2COH$), 1.80 (s, 3, CH_3CONH), 3.40 (t, 2, CH_2N), 3.73 (dd, J = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.10 (m, 1, C-4 *H* cis to C-5 *H*), 4.70 (m, 1, C-5 *H*), 7.43 (s, 4, aromatic), and 8.27 (m, 1, CH_3CONH). Anal. ($C_{15}H_{20}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[4-(1-Oxopropyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (36). To a solution of 2.34 g (10 mmol) of **21**[1] in 30 mL of methanesulfonic acid was added 1.4 g of propanoic anhydride followed by 1.01 g of methanesulfonic anhydride, and the mixture was stirred overnight. The solution was then poured onto ice and the resulting solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried (K_2CO_3) and evaporated in vacuo to give 2.4 g (83%) of a white solid, which was crystallized from acetonitrile to yield 1.5 g (52%) of **36**: mp 180–181 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.10 (t, J = 7 Hz, 3, CH_3CH_2CO), 1.87 (s, 3, CH_3CONH), 3.05 (q, J = 7 Hz, 2, CH_3CH_2CO), 3.45 (t, 2, CH_2N), 3.83 (dd, J = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.20 (m, 1, C-4 *H* cis to C-5 *H*), 4.78 (m, 1, C-5 *H*), 7.70 and 8.03 (AB, J = 9 Hz, 4, aryl H), and 8.28 (m, 1, CH_3CONH). Anal. ($C_{15}H_{18}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[4-(1-Oxobutyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (37). To a solution of 5.0 g of phosphorus pentoxide in 75 mL of methanesulfonic acid was added 5.0 g (21.4 mmol) of **21**[1] and then 6.78 g (42.8 mmol) of butanoic anhydride by syringe pump at the rate of 0.75 mL/h. The mixture was stirred overnight and then poured onto ice and the resulting solution was extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried (K_2CO_3) and evaporated in vacuo to give 8.0 g of a colorless residue, which was crystallized from 2-propyl acetate to yield 1.25 g (19%) of **37**: mp 201.5–202.5 °C; ^{1}H NMR (200 MHz, DMSO-d_6/D_2O) δ 1.00 (t, J = 7 Hz, 3, $CH_3CH_2CH_2CO$), 1.68 (s, 2, $CH_3CH_2CH_2CO$) 1.90 (s, 3, CH_3CONH), 3.02 (q, J = 7 Hz, 2, $CH_3CH_2CH_2CO$), 3.50 (t, 2, CH_2N), 3.87 (dd, J = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.24 (m, 1, C-4 *H* cis to C-5 *H*), 4.83 (m, 1, C-5 *H*), and 7.75 and 8.07 (AB, J_{AB} = 9 Hz, 4, aryl H). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[4-(2-Methyl-1-oxopropyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (38). This substance was prepared from **21** and 2-methylpropanoic acid in 21% yield by the procedure described for **36**; mp 129–130.5 °C; $[\alpha]^{25}_D$ = −19.9° ± 2.0° (c = 1.08, ethanol). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[4-(1-Hydroxyethyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (39). To a solution of 2.76 g (10 mmol) of **31**[1] in 50 mL of THF under nitrogen was added a solution of 0.500 g of lithium borohydride in 20 mL of THF. The mixture was stirred for 18 h and then concentrated to dryness in vacuo and treated with water. The pH was adjusted to 4 by addition of HCl and the solid was filtered (1.6 g). The filtrate was adjusted to pH 7 by addition of $NaHCO_3$, saturated with NaCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and evaporated in vacuo to yield an additional 0.700 g. The combined solids were crystallized from acetonitrile/ether to yield 2.3 g (83%) of a mixture of diastereomers of **39**: mp 146–150 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.32 (d, J = 7 Hz, 3, (CH_3CHOH), 1.87 (s, 3, CH_3CONH), 3.43 (t, J = 7 Hz, 2, CH_2N), 3.75 (dd, J = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.13 (dd, J = 8 Hz, J' = 8 Hz, 1, C-4 *H* cis to C-5 *H*), 4.72 (m, 1, C-5 *H*), 5.15 (d, J = 5 Hz, 1, CHO*H*), 7.37 and 7.48 (AB, J_{AB} = 8 Hz, aryl H), and 8.27 (m, 1, CH_3CONH). Anal. ($C_{14}H_{18}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[4-(1-Hydroxypropyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (40). This substance was prepared from **36** by the procedure described for **39**: mp 118–122 °C; $[\alpha]^{25}_D$ = −12.3° ± 0.8° (c = 1.01, ethanol). Anal. ($C_{15}H_{20}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[4-(1-Hydroxybutyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (41). This substance was prepared from **37** by the procedure described for **39**; mp 125–129 °C. Anal. ($C_{16}H_{22}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[4-(1-Hydroxy-2-methylpropyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (42). This substance was prepared from **38** by the procedure described for **39**: mp 172–174 °C. Anal. ($C_{16}H_{22}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[4-(Chloroacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (43). This substance was prepared from **21** and chloroacetic anhydride in 40% yield by the procedure described for **37**: mp 176–177 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.82 (s, 3, CH_3CONH), 3.43 (m, 2, CH_2N), 3.82 (dd, J = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.18 (m, 1, C-4 *H* cis to C-5 *H*), 4.77 (m, 1, C-5 *H*), 5.16 (s, 2, $ClCH_2CO$), 7.72 and 8.03 (AB, J_{AB} = 9 Hz, 4, aryl H), and 8.28 (m, 1, CH_3CONH). Anal. ($C_{14}H_{15}N_2O_4Cl$) C, H, N.

(*S*)-*N*-[[3-[4-(Acetoxyacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (44). A mixture of 1.30 g (4.2 mmol) of **43**, 1.0 g of sodium acetate, and 0.10 g of 18-crown-6 in 235 mL of THF and 25 mL of DMF was heated at 100 °C for 1 h. The mixture was then evaporated to dryness in vacuo and the residue was crystallized from acetonitrile to yield 0.700 g (50%) of **44**: mp 183–184.5 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.80 (s, 3, CH_3CONH), 2.12 (s, 3, CH_3CO_2), 3.42 (m, 2, CH_2N), 3.79 (dd, J = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.17 (m, 1, C-4 *H* cis to C-5 *H*), 4.73 (m, 1, C-5 *H*), 5.41 (s, 2, $CH_3CO_2CH_2CO$), 7.69 and 7.98 (AB, J_{AB} = 8 Hz, 4, aryl H), and 8.25 (m, 1, CH_3CONH). Anal. ($C_{16}H_{18}N_2O_6$) C, H, N.

(*S*)-*N*-[[3-[4-(Bromoacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (45). To 6.54 g (24 mmol) of **31** in 60 mL of acetic acid was added 5 mL of methanesulfonic acid and then 1.25 mL (14 mmol) of bromine and the mixture was stirred until the bromine had been consumed. The mixture was poured into 350 mL of water and the product was filtered and dried to yield 8.0 g; mp 167–169 °C dec. The product was crystallized from methanol; mp 188–189 °C dec. Anal. ($C_{14}H_{15}N_2O_4Br$) C, H, N, Br.

(*S*)-*N*-[[3-[4-(Fluoroacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (46). A. (*R*)-[3-[4-(Bromoacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl Butyrate. To a solution of 5.0 g (16.4 mmol) of (*R*)-[3-(4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl butyrate[1] in 50 mL of $CHCl_3$ at 0 °C was added 2.9 g (18 mmol) of bromine and the mixture was stirred at ambient temperature for 1 h. The solution was washed with saturated aqueous NaCl, dried ($MgSO_4$), and purified by flash column chromatography to afford 3.62 g (57%) of the title compound.

B. (*R*)-[3-[4-(Fluoroacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl Butyrate. A mixture of 2.50 g (6.5 mmol) of the bromoacetyl compound described in part A above, 1.52 g (26.2 mmol) of potassium fluoride, and 0.875 g (3.3 mmol of 18-crown-6 in 25 mL of acetonitrile was heated under reflux for 16 h. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with water and dried (Na_2SO_4), and the product was purified by flash chromatography to give 1.64 g (78%) of the title compound.

C. (*S*)-*N*-[[3-[4-(Fluoroacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (46). The fluoroacetyl compound from part B above was converted to acetamide **46** by the last five steps of Scheme I:[1] mp 165–166 °C; $[\alpha]^{25}_D$ = −43° (c = 1.0, acetonitrile); mass spectrum ($C_{14}H_{15}N_2O_4F$) calcd m/e 294.1014, measured m/e 264.1017 (M^+).

(*S*)-*N*-[[3-[4-[(Acetylamino)acetyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (47). A. (*R*)-[3-[4-(Bromoacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl Azide. To a solution of 13.6 g (52.3 mmol) of (*R*)-[3-(4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl azide[1] in 100 mL of $CHCl_3$ at 0 °C was added 2.8 mL (55 mmol) of bromine and the mixture was stirred at ambient temperature for 15 min. The solvent was removed in vacuo, the residue was triturated with 10% methanol/CH_2Cl_2, the solution was filtered to remove insoluble material, and the solvent was removed in vacuo to give the crude product, which was purified by flash column chromatography to afford 5.8 g (33%) of the title compound.

B. (*R*)-[3-[4-(Azidoacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl Azide. A solution of 2.0 g (5.9 mmol) of the bromoacetyl azide described in part A above and 0.575 g (8.85 mmol) of sodium azide in 8 mL of DMF was stirred at ambient temperature for 1.5 h. The mixture was then poured into water and extracted with CH_2Cl_2, and the CH_2Cl_2 layer was washed with

water, dried ($MgSO_4$), and evaporated in vacuo to afford the crude product, which was purified by flash column chromatography to afford 1.64 g (92%) of the title compound.

C. (*S*)-*N*-[[3-[4-[(Acetylamino)acetyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (47). The azidoacetyl compound from part B above was converted to acetamide **47** by the last two steps of Scheme I:[1] mp 190 °C dec; $[\alpha]^{25}_D = -27°$ (c = 0.6, methanol); mass spectrum ($C_{16}H_{19}N_3O_5$) calcd m/e 333.1324, measured m/e 333.1323 (M^+).

(*S*)-*N*-[[3-[4-(Cyanoacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (48). A. (*S*)-*N*-[[3-[4-[3-(Dimethylamino)-1-oxo-2(*E*)-propenyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. **A.** A suspension of 1.35 g (4.9 mmol) of **31** and 6.5 mL of *N*,*N*-dimethylformamide dimethyl acetal in 25 mL of absolute ethanol was heated under reflux for 16 h. The solvent was then removed in vacuo to yield 2.0 g of crude product, which was crystallized from acetonitrile to give 1.38 g (85%) of the title compound: mp 186–187 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.83 (s, 3, CH_3CONH), 2.92 (s, 3, CH_3N), 3.14 (s, 3, CH_3N), 3.42 (t, J = 5 Hz, 2, CH_2N), 3.79 (dd, J = 9, 9 Hz, 1, C-4 *H* trans to C-5 *H*), 4.16 (t, J = 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.74 (m, 1, C-5 *H*), 5.84 (d, J = 12 Hz, NCH=C*H*CO), 7.60 and 7.95 (AB, J_{AB} = 8.5 Hz, 4, aryl H), 7.70 (d, J = 12 Hz, NC*H*=CHCO), and 8.27 (m, 1, CH_3CONH).

B. (*S*)-*N*-[[3-[4-(5-Isoxazolyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. A solution of 1.32 g (3.98 mmol) of the enamine described in part A above and 0.500 g (4.29 mmol) of hydroxylamine-*O*-sulfonic acid in 15 mL of methanol was stirred at ambient temperature for 4 h. The mixture was then poured into saturated aqueous $NaHCO_3$ solution, and the precipitate was filtered, washed well with water, and dried in vacuo to yield 0.510 g (43%) of the title compound.

C. (*S*)-*N*-[[3-[4-(Cyanoacetyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (48). To a solution of sodium ethoxide in ethanol [prepared by reaction of 60 mg (2.6 mmol) of sodium metal with 10 mL of ethanol] was added 400 mg (1.32 mmol) of the isoxazole described in part B above, and the mixture was stirred at ambient temperature for 3 h and then neutralized by addition of 10% aqueous hydrochloric acid. The solvent was removed in vacuo to afford the crude product, which was purified by flash column chromatography to give 385 mg (97%) of **48**: mp 207 °C dec; $[\alpha]^{25}_D = -40.8°$ (c = 0.6, DMF). Anal. ($C_{15}H_{15}N_3O_4$) C, H, N.

***N*-[[3-[4-(Dimethylamino)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (49). A. 4-(Dimethylamino)benzoyl Azide.** To a solution of 3.30 g (20 mmol) of 4-(dimethylamino)benzoic acid in 100 mL of acetone under nitrogen was added 2.53 g (25 mmol) of triethylamine, and the mixture was cooled to 0–5 °C in an ice bath and treated dropwise with 3.64 g (38.5 mmol) of methyl chloroformate. The resulting mixture was stirred at ambient temperature for 15 min and then cooled to 0 °C again and treated with a cold solution of 2.5 g (38.5 mmol) of sodium azide dissolved in the minimum amount of water (~8 mL) as rapidly as possible at <5 °C. The mixture was stirred at 0 °C for 1 h and then poured into 500 mL of ice/water, and the solid was filtered, washed with cold water, and dried under nitrogen to yield 1.10 g (29%); mp 90–92.5 °C.

B. [3-[4-(Dimethylamino)phenyl]-2-oxo-5-oxazolidinyl]methyl Azide. A solution of 5.0 g (26.3 mmol) of the acyl azide described in part A above and 2.70 g (26.3 mmol) of glycidyl azide[3] in 25 mL of dry xylenes was added dropwise to an azeotropically dried solution of 0.15 g of lithium bromide and 0.38 g of tri-*n*-butylphosphine oxide in 120 mL of xylene at 130–139 °C over a period of 30 min. The mixture was heated under reflux for 1 h after the addition had been completed and then cooled to room temperature, and the solvent removed in vacuo. The residue was triturated with water and the solid was filtered, triturated with hexanes, and dried to give 6.4 g (90%) of a tan solid; mp 110.5–113 °C. This material was suspended in 200 mL of 95% ethanol and hydrogenated in the presence of 0.5 g of platinum oxide under 40 psig of hydrogen for 2.0 h to give, after filtration of the catalyst and removal of solvent in vacuo, 5.14 g (89%) of the amine. This product was dissolved in 200 mL of THF containing 7 mL of triethylamine and treated with 2.8 mL (26 mmol, 20% excess) of acetyl chloride. After stirring for 30 min, the precipitated triethylamine hydrochloride was filtered and the filtrate was concentrated in vacuo to afford 6.1 g of crude product, which was crystallized from acetone to afford 3.7 g (51%) of **49**: mp 150–151 °C; mass spectrum ($C_{14}H_{19}N_3O_3$) calcd m/e 277.1426, measured m/e 277.1437 (M^+). Anal. ($C_{14}H_{19}N_3O_3$) C, H, N.

***N*-[[3-[4-(Diethylamino)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (50).** By the same sequence described for preparation of **49**, 4-(diethylamino)benzoic acid was converted into **50**: mp 128–129 °C; mass spectrum ($C_{16}H_{23}N_3O_3$) calcd m/e 305.1740, measured m/e 305.1741 (M^+). Anal. ($C_{16}H_{23}N_3O_3$) C, H, N.

(*S*)-*N*-[[3-[4(*R*)-(Methylsulfinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (52). To a solution of 3.42 mL of diethyl *L*-(+)-tartrate and 3.0 mL of tetra-2-propyl titanate in 100 mL of dry CH_2Cl_2 at −15 °C under nitrogen was added 0.15 mL of water, and the mixture was stirred for 20 min. Then 2.80 g (10 mmol) of **51**[1] was added, and the mixture was cooled to −20 °C. After homogenous solution had been achieved, a solution of 1.0 mL of 90% *tert*-butyl hydroperoxide in 25 mL of CH_2Cl_2 was added dropwise over the period of 5 min. The mixture was stirred at −15 °C to −20 °C for 2 h, then 10 mL of water was added, and the mixture was stirred for 1 h at −20 °C and then at ambient temperature for 1 h. Insoluble material was filtered, the solvent was removed from the filtrate in vacuo, and the residue was dissolved in 97:3 chloroform/methanol and purified by flash column chromatography followed by two crystallizations from acetonitrile/2-propyl acetate to yield 0.800 g (27%) of **52**: mp 175.5–176 °C; $[\alpha]^{25}_D = +20.5° \pm 0.8°$ (c = 1.0, water). Anal. ($C_{13}H_{16}N_2O_4S$) C, H, N, S. The analysis of the enantiomeric excess of the product was carried out with Kagan's chiral shift reagent[6] and found to be >90%.

(*S*)-*N*-[[3-[4(*S*)-(Methylsulfinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (53). By the same procedure described above for preparation of **52** but with *R*-(−)-diethyl tartrate, **51** afforded 1.82 g (47%) of **53**: mp 185–186 °C; $[\alpha]^{25}_D = -117° \pm 0.8°$ (c = 1.0, water). Anal. ($C_{13}H_{16}N_2O_4S$) C, H, N, S. The analysis of the enantiomeric excess of the product was carried out with Kagan's chiral shift reagent[6] and found to be >90%.

(*S*)-*N*-[[3-[4-[(Fluoromethyl)thio]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (54). To a solution of 2.0 g (6.75 mmol) of **72**[1] in 20 mL of CH_2Cl_2 was added 1.65 mL (13.5 mmol) of (*N*,*N*-diethylamido)sulfur trifluoride (DAST) and the mixture was heated at 50 °C for 2 h. The reaction mixture was then poured into saturated $NaHCO_3$ solution and the aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ layers were washed with saturated NaCl and dried (Na_2SO_4) and the product was purified by flash column chromatography to give 1.29 g of **54** containing some **51**.

(*S*)-*N*-[[3-[4-(Chlorosulfonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (55). To 40 mL of chlorosulfuric acid at 0 °C under nitrogen was added with stirring 10.0 g (43 mmol) of **21**. The mixture was stirred at room temperature for 1 h and then poured into ice with good stirring (**caution**: splatters!) and the solid was filtered and dried on the filter under nitrogen. Isolated was 11.85 g (83%): mp 119–121 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.83 (s, 3, CH_3CONH), 3.43 (m, 2, CH_2N), 3.76 (dd, J = 8, 8 Hz, 1, C-4 *H* trans to C-5 *H*), 4.13 (m, 1, C-4 *H* cis to C-5 *H*), 4.73 (m, 1, C-5 *H*), 7.50 and 7.60 (AB, J_{AB} = 7 Hz, 4, aryl H), and 8.29 (m, 1, CH_3CONH).

(*S*)-*N*-[[3-(4-Mercaptophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (56). To a solution of 4.0 g (12 mmol) of **55** in 50 mL of acetic acid was 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 and then cooled and filtered, and the solvent was removed in vacuo. The residue was cooled and triturated with water and filtered to give 2.92 g (79%) of (*S*)-*N*-[[3-[4-(acetylthio)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 138.5–139.5 °C. The *S*-acetyl group was hydrolyzed by using the following procedure: To a suspension of 2.92 g (9.5 mmol) of the ester 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

(6) Deshmukh, M.; Dunbach, E.; Juge, S.; Kagan H. B. *Tetrahedron Lett.* **1984**, *32*, 3467.

had been consumed (TLC) and then evaporated in vacuo and triturated with water which had been acidified by addition of a little acetic acid, chilled, and filtered to yield 2.53 g (100%) of **56**; mp 205–209 °C.

(*S*)-*N*-[[3-[4-[(Trifluoromethyl)thio]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (57). To a solution of 7.8 g (29.3 mmol) of **56** in 40 mL of liquid ammonia was added 7.0 g (35 mol) of trifluoromethyl iodide, and the mixture was stirred at −33 °C for 1 h under irradiation from an ultraviolet sunlamp. The liquid ammonia was then allowed to distill, the residue was treated with ice water, and the solid was filtered and purified by flash column chromatography to afford 3.2 g (33%) of **57**: mp 172.5–173.5 °C; $[\alpha]^{25}_D = -17°$ (c = 1.0, ethanol). Anal. ($C_{13}H_{13}F_3N_2O_3S$) C, H, N.

(*S*)-*N*-[[3-[4-(Ethylsulfinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (58). To a solution of 1.47 g (5 mmol) of **18** in 100 mL of methylene chloride at −30 °C (acetone bath containing just enough dry ice to cool to −30 °C) under nitrogen was added 1.015 g (5 mmol) of 85% *m*-chloroperbenzoic acid, and the mixture was stirred at −30 °C for 30 min and then allowed to stir and warm slowly. When the temperature reached −20 °C, starch iodide paper indicated that all the oxidant had been consumed. The mixture was then evaporated to dryness in vacuo and the residue was triturated with 200 mL of ether under nitrogen until the solid was crystalline. Filtration and crystallization from benzene/methanol yielded 1.05 g (67%) of **58**: mp 109–110 °C; $[\alpha]^{25}_D = -19.4° \pm 2.0°$ (c = 1.06, ethanol). Anal. ($C_{14}H_{18}N_2O_4S$) C, H, N, S.

(*S*)-*N*-[[3-[4-(*n*-Propylsulfinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (59). By the same procedure described for preparation of **58**, **19** was oxidized to **59** (1.196 g, 75%: mp 160–162 °C; $[\alpha]^{22}_D = -15.4° \pm 2.0°$ (c = 1.00, ethanol). Anal. ($C_{15}H_{20}N_2O_4S$) C, H, N, S.

(*S*)-*N*-[[3-[4-[(Fluoromethyl)sulfinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (60). To a solution of 1.0 g (3.35 mmol) of **54** in 20mL of CH_2Cl_2 at 0 °C was added 0.715 g (3.52 mmol) of *m*-chloroperbenzoic acid, and the mixture was stirred at 0 °C for 1 h and then at ambient temperature for 16 h. The mixture was then treated with saturated aqueous Na_2SO_3 solution, and the CH_2Cl_2 layer was washed with 1 N aqueous sodium hydroxide solution and saturated NaCl, then dried (Na_2SO_4), and purified by flash column chromatography to give 0.158 g (15%) of **60**: mp 150–151.5 °C; $[\alpha]^{25}_D = -26.5°$ (c = 0.61, methanol). Anal. ($C_{13}H_{15}FN_2O_4S$) C, H, N.

(*S*)-*N*-[[3-[4-[(Trifluoromethyl)sulfinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (61). A solution of 1.8 g (5.4 mmol) of **57** and 1.18 g (5.66 mmol) of *m*-chloroperbenzoic acid in 50 mL of CH_2Cl_2 was stirred at ambient temperature for 60 h. The mixture was then worked up as described for **60** to yield 1.24 g (66%) of **61**: mp 135–136 °C; $[\alpha]^{25}_D = -16°$ (c = 1.0, ethanol). Anal. ($C_{13}H_{13}F_3N_2O_4S$) C, H, N.

(*S*)-*N*-[[3-[4-(Ethylsulfonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (62). To a suspension of 1.47 g (5 mmol) of **18** in 100 mL of methylene chloride at ambient temperature under nitrogen was added 2.05 g (10 mmol) of 85% *m*-chloroperbenzoic acid, and the mixture was stirred until all the peracid had been consumed. Then small portions of additional peracid were added until an excess was present and the mixture was stirred for 20 min to ensure that the oxidation was complete. The mixture was then evaporated to dryness in vacuo and the residue was triturated with 200 mL of ether under nitrogen and the product was filtered to afford 1.556 g (95%) of **62**. The product was crystallized from benzene/chloroform to yield 0.945 g (58%): mp 168–170 °C; $[\alpha]^{25}_D = -27.6° \pm 2.0°$ (c = 1.00, methanol). Anal. [$C_{14}H_{18}N_2O_5S$) C, H, N, S.

(*S*)-*N*-[[3-[4-(*n*-Propylsulfonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (63). By the same method described above for the preparation of **62**, 1.54 g (5 mmol) of **19** afforded 1.275 g (75%) of **63**: mp 160.5–161 °C; $[\alpha]^{25}_D = -23.6° \pm 2.0°$ (c = 1.00, ethanol). Anal. ($C_{15}H_{20}N_2O_5S$) C, H, N, S.

(*S*)-*N*-[[3-[4-[(Fluoromethyl)sulfonyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (64). By the same method described above for the preparation of **62**, 2.02 g (6.77 mmol) of **54** afforded 0.740 g (32%) of **64**: mp 104–106 °C; $[\alpha]^{25}_D = -27.6°$ (c = 0.61, methanol). Anal. ($C_{13}H_{15}FN_2O_5S$) C, H, N.

(*S*)-*N*-[[3-[4-[(Trifluoromethyl)sulfonyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (65). A solution of 1.20 g (3.6 mmol) of **57** and 1.88 g (9 mmol) of *m*-chloroperbenzoic acid was heated under reflux for 16 h. The mixture was then washed with saturated $NaCO_3$ solution and saturated NaCl, dried (Na_2SO_4), and purified by flash column chromatography to yield 1.33 g (100%) of **65**: mp 142–144 °C; $[\alpha]^{25}_D = -18°$ (c = 1.00, ethanol). Anal. ($C_{13}H_{13}F_3N_2O_5S$) C, H, N.

(*S*)-*N*-[[3-[4-(2-Oxopropyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (66). A mixture of 3.60 g (10 mmol) of **22**, 6.91 g (50 mmol) of the potassium salt of 2,4-pentanedione, and 1.90 g of cuprous iodide in 30 mL of DMF was heated under nitrogen at 100 °C for 6 h. Then the cooled mixture was diluted with 10 mL of water and acetic acid, and hydrogen sulfide was bubbled through the mixture until copper sulfide precipitation was complete. The resulting mixture was filtered through diatomaceous earth, the solvent was removed in vacuo, and the residue purified by flash column chromatography to yield 0.220 g (7.6%) of **66**: mp 78.5–80.5 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.83 (s, 3, CH_3CONH), 2.13 (s, 3, CH_3COCH_2), 3.42 (t, J = 5 Hz, 2, CH_2N), 3.75 (2, s, CH_3COCH_2), 3.75 (m, 1, C-4 *H* trans to C-5 *H*), 4.12 (t, J = 9 Hz, 1, C-4 *H* cis to C-5 *H*), 4.72 (m, 1, C-5 *H*), 7.22 and 7.48 (AB, J_{AB} = 7 Hz, 4, aryl H), and 8.27 (m, 1, *H*NCOCH$_3$). Anal. ($C_{15}H_{18}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-[4-[(Hydroxyimino)methyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (67). A mixture of 3.00 g (11.4 mmol) of **26**, 1.59 g (22.8 mmol) of hydroxylamine hydrochloride, and 3.17 g (22.8 mmol) of potassium carbonate in 50 mL of CH_2Cl_2 was stirred with heating for 1 h and then poured into water, the CH_2Cl_2 layer was separated, dried ($MgSO_4$), evaporated in vacuo, and the residue crystallized from acetonitrile to yield 1.10 g (35%); mp 206–207.5 °C. Anal. ($C_{13}H_{15}N_3O_4$) C, H, N.

(*S*)-*N*-[[3-[4-[1-(Hydroxyimino)ethyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (68). By the same method described for the preparation of **67**, 3.00 g (10.8 mmol) of **31** afforded 1.91 g (61%) of **68**; mp 210–212 °C. Anal. ($C_{14}H_{17}N_3O_4$) C, H, N.

(*S*)-*N*-[[3-[4-[1-(Hydroxyimino)butyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (69). By the same method described for the preparation of **67**, 3.04 g (10 mmol) of **37** afforded 1.93 g (60%) of **69**; mp 163–164 °C. Anal. ($C_{16}H_{21}N_3O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Aminophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (70). To a solution of 5.00 g (17.9 mmol) of **9** in 50 mL of absolute ethanol under nitrogen was added 15 mL of a slurry of Raney nickel in water, and the mixture was heated to 50 °C and treated dropwise with a solution of 5 mL of 95% anhydrous hydrazine in 20 mL of ethanol. The temperature slowly rose to reflux with copious gas evolution. The mixture was heated under reflux for 0.5 h and then filtered and concentrated in vacuo to afford 4.4 g of crystalline material, which was crystallized from acetonitrile to afford 3.42 g (77%) of **70**; mp 147.5–148.5 °C. Anal. ($C_{12}H_{15}N_3O_3$) C, H, N.

In Vitro Susceptibility Tests. MICs of the compounds for the various bacterial strains were determined by a microtiter broth dilution assay as detailed previously.[1] For comparative purposes, MICs of racemic compounds were divided by two to reflect the fact that only one oxazolidinone enantiomer possesses antibacterial activity.