Tetrahedron Vol. 44, No. 11, pp. 3119 to 3126, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00
© 1988 Pergamon Press plc

1,3-DIPOLAR CYCLOADDITION REACTIONS OF PYRAZOLIDINIUM YLIDES WITH VINYL SULFONES. A REGIOSELECTIVE SYNTHESIS OF BICYCLIC PYRAZOLIDINONE ANTIBACTERIAL AGENTS

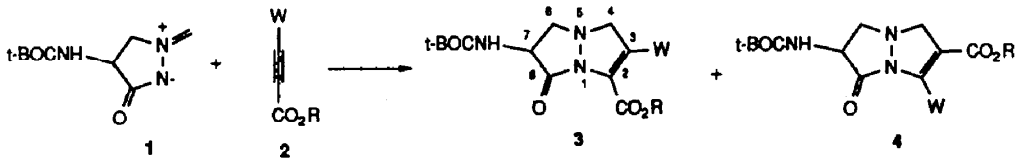
Louis N. Jungheim*, Charles J. Barnett*, Joseph E. Gray,
Linus H. Horcher, Timothy A. Shepherd, and Sandra K. Sigmund

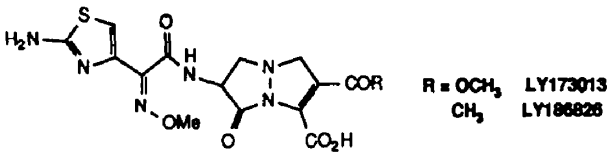
Eli Lilly & Company
Lilly Research Laboratories
Indianapolis, IN 46285

(*Received in USA* 29 *September* 1987)

Abstract - The 1,3-dipolar cycloaddition reaction of pyrazolidinium ylide 1 with substituted vinyl sulfones 5 was studied. Elimination of benzenesulfinic acid from the resulting cycloadducts gave rise to bicyclic pyrazolidinones 3. The (E)-olefin isomers were found to undergo cycloaddition in a highly regioselective fashion. These pyrazolidinones 3 represent the nuclei of an exciting new class of potent antibacterial agents that mimic β-lactams.

In several earlier publications[1] we have described the 1,3-dipolar cycloaddition chemistry of pyrazolidinium ylide 1 with propiolate esters 2. The bicyclic pyrazolidinones 3 and 4 thus obtained represent the nuclei of an exciting new class of γ-lactam antibacterial agents, exemplified by LY173013 and LY186826.





Unfortunately, this synthetic approach suffers from a general lack of regiocontrol (Table I). Frequently both isomeric products 3 and 4 are obtained and the desired isomer 3 is often the minor product.[1c] This is especially true for the synthesis of LY173013 and LY186826 where the required nuclei 3a and 3b are obtained in disappointing yield. The desire to prepare large quantities of these compounds for further biological evaluation has prompted us to search for a regiocontrolled synthesis of these novel bicyclic compounds.

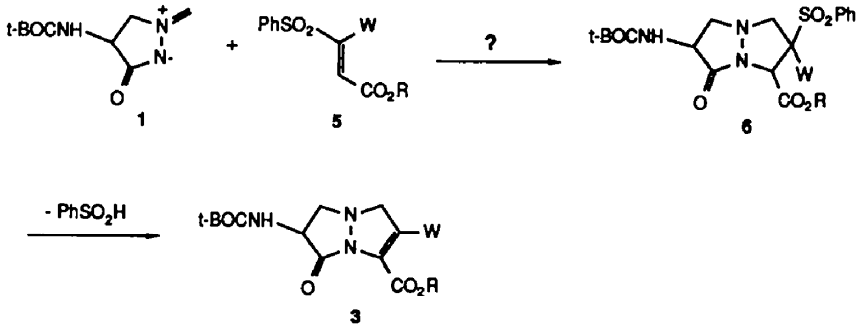
In our earlier work we noted that propiolate esters substituted with strong electron-withdrawing groups were most likely to give acceptable yields of the desired regioisomer 3[1c], when reacted with ylide 1. We reasoned that a vinyl sulfone, e.g. 5, should selectively undergo 1,3-dipolar cycloaddition with 1 to give adduct 6. Base-catalyzed elimination of the elements of benzenesulfinic acid would then give the desired bicyclic pyrazolidinone

Dedicated to Professor Edward C. Taylor on the occasion of his 65th birthday.

Table I. Cycloaddition of Ylide 1 with Propiolate Esters 2[a].

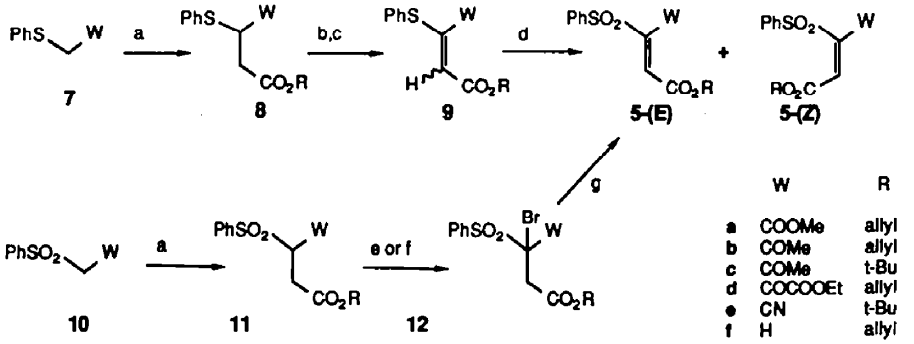
Acetylene	W	R	Ratio 3:4	Yield %
2a	CO_2Me	allyl	50:50	38
2b	COMe	allyl	40:60	26
2f	H	allyl	100:0	23

a. Taken from reference 1c.



nucleus 3. Paquette[2] has used phenyl vinyl sulfones as acetylene equivalents in [4+2]π cycloaddition reactions. There have been a number of reports on the regioselective 1,3-dipolar cycloaddition reactions of di-substituted vinyl sulfones[3]. In practice, we have found that this approach provides a variety of bicyclic pyrazolidinones 3 in a highly regioselective fashion. Also, significantly improved chemical yields were obtained, relative to the acetylene addition route.

Vinyl sulfones 5a,c were prepared by extension of a recently reported vinyl sulfoxide synthesis.[4] For example, alkylation of 7c with t-butyl bromoacetate, chlorination of the resulting sulfide 8c (N-chlorosuccinimide), followed by base-catalyzed elimination of HCl, provided a mixture of vinyl sulfides 9c. The predominant isomer (ratio 3:2) was assigned the (E)-configuration on the basis of its higher field vinyl signal (δ5.30) as compared to that of the minor isomer (δ6.18). This trend in chemical shifts has been reported for analogous vinyl sulfides.[5] Peracid oxidation of the vinyl sulfide mixture afforded a 3:2 mixture of sulfones 5c, which could be separated by silica chromatography, albeit in low recovery, apparently due to degradation on the column. The major sulfone isomer possessed the (E)-configuration based on the sulfide assignments.

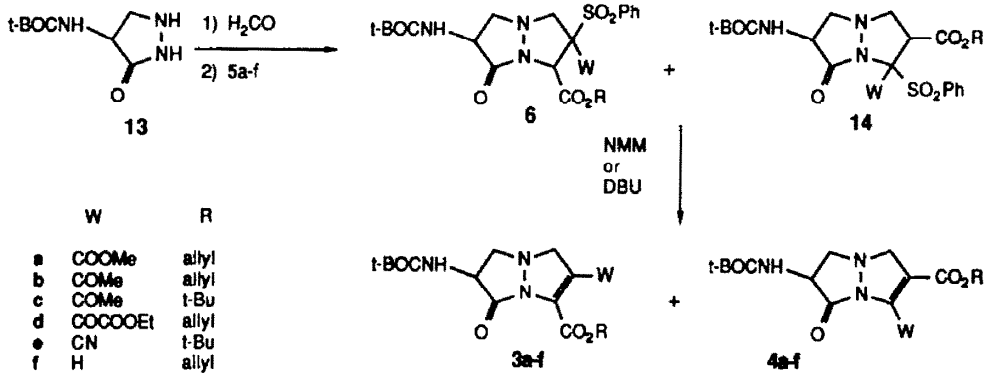


a) $BrCH_2CO_2R$, NaH, THF; b) NCS, dioxane; c) DBU, CH_2Cl_2; d) MCPBA
e) Br_2, Et_3N, $CHCl_3$ -20 ; f) NBS, CCl_4; g) Et_3N or DBU / ether

Although it was possible, in principle, to prepare all the sulfones 5 by this procedure, we were interested in developing a stereoselective preparation of the (E)-isomers, in view of the more desirable regiochemical results obtained with the (E)-vinyl sulfones in the cycloaddition step (Table II). We noted that a literature procedure[6] for preparing 5f from allyl 2,3-dibromopropionate and sodium p-toluenesulfinate proceeded stereoselectively, apparently via β-elimination of the intermediate 2-bromo-3-(p-tolylsulfonyl)propanoate to give exclusively the (E)-isomer[7] (NMR vinyl protons J=16 Hz). We anticipated that the bulky arylsulfonyl substituent would exert a similar influence on eliminations of α-halosulfones, e.g. 12. Accordingly, alkylation of phenylsulfonyl-2-propanone (10b) with allyl bromoacetate afforded sulfone 11b. Exposure of 11b to one equivalent of bromine in the presence of two equivalents of triethylamine[8](20°C) gave rise to 5b-(E) as a single isomer (100% crude yield); apparently via in situ elimination of the initial bromination product 12b, with remarkable chemo- and stereoselectivity. Comparison of the NMR vinyl signals of 5b thus obtained (δ6.86) with the t-butyl ester 5c-(E) obtained from vinyl sulfide oxidation (δ6.76) confirmed the stereochemical assignment. Similarly, carbethoxycarbonyl-substituted 5d-(E) was obtained as a single isomer.

Limitations of the sulfone halogenation-elimination strategy are illustrated by the following examples. The bromination of cyanosulfone 11e could not be carried out with Br_2/Et_3N, but was successfully accomplished with N-bromosuccinimide. Elimination of the resulting bromosulfone 12e under carefully controlled conditions (DBU, -78°C) afforded 5e-(E), whereas an isomeric mixture (E:Z=3:2) was obtained with DABCO at 0°C. The carbomethoxysulfone 5a could not be prepared by this method because bromination of the sulfone 11a failed with both bromine and NBS.[9]

Ylide 1 was generated in situ by reacting pyrazolidinone 13 with aqueous formaldehyde in 1,2-dichloroethane. Addition of a vinyl sulfone 5 to this mixture followed by refluxing for several hours gave rise to cycloadducts 6 and 14. Typically these were not isolated, but



	W	R
a	COOMe	allyl
b	COMe	allyl
c	COMe	t-Bu
d	COCOOEt	allyl
e	CN	t-Bu
f	H	allyl

rather the reaction mixture was treated with either N-methylmorpholine (NMM) or DBU at 0°C to ambient temperature. Elimination of the sulfonyl moiety gave predominantly the desired pyrazolidinones 3a-f. The regiochemistry of 3 and 4 was assigned by NMR and UV spectra.[1c]. Structures of 3a[1b] and 3b[1c] have been confirmed by X-ray crystallography. These results are summarized in Table II.

Table II. Cycloaddition of Ylide 1 with Vinyl Sulfones 5.

Olefin	W	R	Ratio 3:4[a]	Yield %
5a-(E)	CO_2Me	allyl	97:3[b]	47
5b-(E)	COMe	allyl	98:2[b]	61[d]
5c-(E)	COMe	t-Bu	98:2[b]	32
5c-(Z)	COMe	t-Bu	5:95	28
5d-(E)	$COCO_2Et$	allyl	100:0	38
5e-(E)	CN	t-Bu	100:0	44
5e-(E:Z)=3:2	CN	t-Bu	86:14	43
5f-(E)[c]	H	allyl	100:0	49

a. Determined by NMR integration of the crude reaction mixtures. b. Ratio also measured by reverse phase HPLC. c. Toluenesulfonyl was employed instead of a benzenesulfonyl moiety in this example. d. The (S)-isomer of 13 was used in this experiment.

It is interesting to note that the (E)-olefins are highly selective for the formation of 3, while the (Z)-isomer is less selective; and in the case of 5c a reversal in selectivity is observed. Experimentally the (Z)-isomers appear to react more sluggishly than the (E)-isomers.[10] Caramella[3a] has reported differences in regioselectivity for the cycloaddition of (E) and (Z)-styryl sulfones with nitrile oxides.

Bicyclic pyrazolidinone 3b can be prepared in optically active form by starting with enantiomerically pure[11] pyrazolidinone 13 and using N-methylmorpholine (DBU causes racemization) to eliminate the sulfone moiety. The product was shown to be enantiomerically pure by deprotection (3N HCl/dry HOAc) and acylation, by the method of Mosher[12], to give a single diastereomer.

We have found this approach to be a substantial improvement over the acetylene cycloaddition methodology. Vinyl sulfones 5a-f provide pyrazolidinones 3a-f in a highly regioselective fashion and in higher overall yield than the acetylene cycloaddition approach. In addition, several new nuclei, e.g. 3d,e,[13] have been synthesized which were not prepared by the acetylene cycloaddition route. The use of this chemistry to expand the SAR of this exciting new class of antibacterial agents will be the subject of a future report.

Experimental Section

NMR spectra were obtained on a Jeol FX-90Q, Brüker Corp, 270 MHz or on a General Electric QE-300 instrument. Field desorption mass spectra (F.D.M.S.) were taken on a Varian-MAT 731 Spectrometer with carbon dendrite emitters. Flash chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh). Preparative HPLC was carried out on a Waters Prep 500 system. Analytical HPLC was carried out on C_{18} (Waters μ-bondpak) eluting with CH_3CN/Water 1:1 with 1% HOAc. Melting points are uncorrected.

Allyl (E)-2-carbomethoxy-2-phenylsulfonylacrylate (5a)

A solution of allyl (E)-2-carbomethoxy-2-phenylsulfinyl-acrylate[4] (147 mg, 0.50 mmol) and 85% m-chloroperbenzoic acid (106 mg, 0.53 mmol) in CH_2Cl_2 (10ml) was stirred at room temperature overnight. An additional 20 mg of m-CPBA was added and the mixture stirred 1h. This solution was washed with aqueous sodium metabisulfite, 5% aqueous sodium bicarbonate, water, and brine. Drying (Na_2SO_4) and evaporation of solvent afforded 134 mg of crude sulfone. NMR (90 MHz, $CDCl_3$): δ7.9-7.4 (m,5,aryl); 7.13 (s,1,vinyl); 5.44-5.18(m,2); 4.68 (dm,2); 3.78 (s,3,OCH_3).

Allyl 3-(phenylsulfonyl)-4-oxopentanoate (11b).

To a suspension of sodium hydride (6.41g, 0.267 mol) in dry THF (125 ml) at -15° was added phenylsulfonyl-2-propanone[14] (50g, 0.253 mol) over 1h. After stirring 20 min, allyl bromoacetate (47.5 g, 0.265 mol) in THF (100 ml) was added over 30 min keeping the reaction mixture below 0°C. The mixture was kept at -5°C for 15 min, then warmed to room temperature overnight. The mixture was poured into saturated aqueous ammonium chloride (800 ml) and $CHCl_3$ (500 ml). The aqueous phase was extracted with $CHCl_3$ (2 x 200 ml) and the combined organic extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent and

crystallization of the oily residue from ethyl acetate/hexanes afforded 52.9g (71%) of 11b, m.p. 62-64°C. NMR (90 MHz, $CDCl_3$): δ7.8-7.4 (m,5,aryl); 6.0-5.58 (m,1); 5.19-5.10 (m,2); 4.65 (m,1); 4.51 (dm,2,J=6); 2.97 (m,2); 2.51 (s,3). F.D.M.S.: 296,232(100). Anal. calcd. for $C_{14}H_{16}O_5S$: C,56.74; H,5.44; found: C,56.83;H,5.24.

Allyl (E)-3-(phenylsulfonyl)-4-oxopent-2-enoate (5b-(E)).

To a -20°C solution of 11b (42g, 0.142 mol) and triethylamine (28.6g, 0.283 mol) in $CHCl_3$ (400 ml) was added bromine (22.6g, 0.141 mol) in $CHCl_3$ (238 ml) over 1 h. The solution was stirred an additional 30 min at -20°C then warmed to room temperature overnight. The mixture was washed with water, 0.5 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (Na_2SO_4) and concentrated in vacuo to afford 41.76g (100% crude) 5b-(E) as an oil which was unstable to silica chromatography and distillation. NMR (90 MHz, $CDCl_3$): δ7.85-7.42 (m,5,aryl); 6.86 (s,1,vinyl); 6.10-5.65 (m,1); 5.44-5.20 (m,2); 4.65 (dm,2,J=6); 2.50 (s,3). F.D.M.S.: M^+=294, 238, 189. IR ($CHCl_3$): 1727 cm^{-1}.

t-Butyl 3-phenylthio-4-oxopentanoate (8c).

To a suspension of NaH (9.6g, 0.24 mol) in dry THF (100 ml) at -10°C was added phenylthio-2-propanone[15] in THF (150 ml) keeping the reaction mixture below -5°C. To the resulting solution was added t-butyl bromoacetate (47.11g, 0.24 mol) in THF (50 ml). The mixture was stirred at 0° for 5h then partitioned between $CHCl_3$ (500 ml) and saturated aqueous ammonium chloride (500 ml). The aqueous layer was extracted with $CHCl_3$ (3 x 250 ml), the combined organic extracts dried (Na_2SO_4) and concentrated to a yellow oil. This material was taken up in hexanes (500 ml) and the resulting crystalline product was collected by filtration affording 36.3g (57%) of 8c, m.p. 81-83°C. A second crop yielded 5.4g, m.p. 80-83°C (total yield: 65%). NMR (90 MHz, $CDCl_3$): δ7.5-7.3 (m,5); 3.95 (dd,1,J=4.5,8); 2.77 (d,1,J=9); 2.66 (d,1,J=6); 2.36 (s,3). F.D.M.S.: M^+ = 280. Anal. calcd. for $C_{15}H_{20}O_3S$: C,64.26; H,7.19; found: C,64.27,H,6.98.

t-Butyl 3-phenylthio-4-oxo-2-pentenoate (9c).

A mixture of 8c (28g, 0.1 mol) and N-chlorosuccinimide (13.6g, 0.1 mol) in THF (150 ml) and CCl_4 (300 ml) was refluxed 6h then stirred at room temperature overnight. The solvent was removed in vacuo and the residue taken up in hexanes (200 ml) and filtered. The solid was washed with hexanes (2 x 50 ml) and the combined filtrates concentrated in vacuo affording 29.7g (94%) of the 3-chloro-derivative which was utilized without purification. NMR (90 MHz, $CDCl_3$): δ7.56-7.3 (m,5); 3.11 (ABq,2,J=16); 2.36 (s,3); 1.41 (s,9).

To a -78° solution of this 3-chloro-derivative (29.7g, 94.4 mmol) in CH_2Cl_2 (150 ml) was slowly added DBU (15g, 94.6 mmol) in CH_2Cl_2 (50 ml), maintaining the temperature <-65°C. After 30 min the mixture was warmed to room temperature. After 5h the reaction mixture was washed with 0.5N hydrochloric acid (2 x 300 ml), then dried (Na_2SO_4) and evaporated, affording 26.6g of crude 9c. NMR ($CDCl_3$, partial): δ5.30 (s, E vinyl) and 6.18 (s, Z vinyl) E/Z=3/2 by integration. Several small scale experiments gave varying isomer ratios ranging from 3/2 to 5/1, E/Z.

t-Butyl 3-phenylsulfonyl-4-oxo-2-pentenoate (5c).

A solution of 9c (5.06g, 18.2 mmol, 3:2 mix of isomers) in CH_2Cl_2 (225 ml) was treated with m-CPBA (8.26g, 40.7 mmol) and stirred at room temperature for 48 hr. The mixture was washed with sodium metabisulfite solution, 5% aqueous sodium carbonate, water, brine, dried (Na_2SO_4) and evaporated. Flash chromatography (CH_2Cl_2) gave 736 mg of pure 5c-(E) as the less polar isomer. NMR (90 MHz, $CDCl_3$): δ7.85-7.4 (m,5,aryl); 6.76 (s,1,vinyl); 2.51 (s,3); 1.46 (s,9). Later eluting fractions contained 5c-(Z) but this material was not of aufficient purity for further transformations.[16] Isomer 5c-(Z) was prepared by treating t-butyl (Z)-3-phenylsulfinyl-4-oxo-2-pentenoate[4,16] (160 mg, 0.54 mmol) with m-CPBA (138 mg, 0.68 mmol) in CH_2Cl_2 (10 ml) at room temperature overnight. Workup as above gave 160 mg (89%) of 5c-(Z). NMR (90 MHz, $CDCl_3$): δ7.9-7.6 (m,5,aryl) 7.44 (s,1,vinyl); 2.40 (s,3); 1.38 (s,9).

Ethyl 2-oxo-3-phenylsulfonyl-4-carboallyloxybutanoate (11d).

To a 0°C solution of 10d[17] (7.5g, 29.3 mmol) in 30 ml of dry DMF was added sodium hydride (1.3g, 29.8 mmol, 55% oil dispersion). After 2h at 0°C allyl bromoacetate (4.4 ml, 29.3 mmol) was added and the mixture allowed to warm to RT. The reaction mixture was diluted with ether, washed several times with water, then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. HPLC of the resulting oil on a Waters Prep 500 system eluting with a gradient of 0 → 40% ethyl acetate in hexanes gave 1.6g pure 11d as a colorless oil and 4.4g of less pure alkylation product. NMR (300 MHz, $CDCl_3$): δ7.80 (d,2,J=8); 7.72 (t,1,J=8); 7.58 (t,2,J=8); 5.8 (m,1); 5.62 (dd,1,J=5,10); 5.22 (m,2); 4.50 (d,2,J=6); 4.29 (q,2,J=8); 3.2-3.0 (m,2); 1.35 (t,3,J=8). IR ($CHCl_3$): 1735, 1216 cm^{-1}. UV (EtOH) λ_{max} 215 (ε8564), 237 (ε6344), 265 (ε4050), 272 (ε3899). F.D.M.S.: M^+=354.

Ethyl (E)-2-oxo-3-phenylsulfonyl-4-carboallyloxybut-3-enoate (5d-(E)).

To a 0°C solution of 11d (0.8g, 2.26 mmol) in $CHCl_3$ (10 ml) was added triethylamine (0.63 ml, 4.52 mmol). The mixture was cooled to -40°C and a solution of bromine (0.36g, 2.26 mmol) in chloroform (10 ml) was added dropwise. The mixture was stirred at -40°C for 90 min then diluted with CH_2Cl_2 and ice water. The organic phase was washed with cold 1N hydrochloric acid, saturated aqueous sodium bicarbonate, and brine. Drying (Na_2SO_4), filtration, and concentration in vacuo gave 0.75g of a yellowish tinted oil which was used without purification. NMR (300 MHz, $CDCl_3$): δ7.86 (d,2,J=7); 7.72 (t,1,J=7); 7.60 (t,2,J=7); 7.15 (s,1); 5.85 (m,1); 5.30 (t,2,J=10); 4.63 (d,2,J=6); 4.28 (q,2,J=9); 1.30 (t,3,J=9).

t-Butyl 3-cyano-3-phenylsulfonylpropanoate (11e).

To a -25°C suspension of NaH (4.9g, 0.123 mol) in dry THF (250 ml) was added phenylsulfonyl acetonitrile (20 g, 0.111 mol) in THF (150 ml) over 30 min. To the resulting mixture was added t-butyl bromoacetate in THF (100 ml) over 35 min. The mixture was poured into saturated ammonium chloride (400 ml) and $CHCl_3$ (400 ml). The aqueous phase was extracted with $CHCl_3$ (250 ml) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting oil (34.5g) was crystallized from ethyl acetate/hexanes to give 19.5g (60%) of 11e. Recrystallization (EtOAc/hexane,1:3) gave 15g of 11e. An analytical sample was obtained by preparative HPLC (silica, hexane:EtOAc 85:15), m.p. 104-105°C. NMR (90 MHz, $CDCl_3$): δ8.1-7.5 (m,5); 4.52 (dd,1,J=4.5,10); 3.20 (dd,1,J=4.5,16); 2.79 (dd,1,J=10,19); 1.47 (s,9). IR ($CHCl_3$): 2250, 1731 cm^{-1}. Anal. calcd. for $C_{14}H_{17}NO_4S$: C,56.93; H,5.80; N,4.74; found: C,57.11; H,5.86; N,4.60.

t-Butyl 3-bromo-3-cyano-3-phenylsulfonylpropanoate (12e).

A mixture of 11e (2.0g, 6.78 mmol), N-bromosuccinimide (1.26g, 7.0 mmol) and AIBN (60 mg) in CCl_4 (40 ml) was refluxed for 6h at which time HPLC analysis (C_{18}, MeCN-H_2O 1:1) indicated complete reaction. The reaction mixture was cooled, filtered and the filtrate concentrated in vacuo, affording 2.79g of 12e as an oil. NMR (90 MHz, $CDCl_3$): δ8.1 (dm,2,J=7); 7.9-7.5 (m,3); 3.41 (ABq,2,J=16); 1.51 (s,9). This material was subjected to elimination without further purification, 96% purity by HPLC (integrated area %).

t-Butyl (E)-3-cyano-3-phenylsulfonylacrylate (5e-(E)).

To a -78°C solution of bromide 12e (0.53g, 1.41 mmol) in ether (50 ml) was added dropwise DBU (0.23 ml, 1.55 mmol) in ether (10 ml) keeping the reaction temperature <-70°C. After 1h the mixture was warmed to -10°C. The mixture was diluted with ether, washed with 0.2N hydrochloric acid, water, brine, then dried (Na_2SO_4), and concentrated in vacuo to give 282 mg 5e-(E) which was used without further purification. NMR (300 MHz, $CDCl_3$): δ8.16-8.01 (m,2); 7.90-7.67 (m,3); 7.43 (s,1); 1.47 (s,9).

Preparation of 5e-(E) and (Z). To a 0°C solution of bromide 12e (0.27g, 0.72 mmol) in ether (10 ml) was added DABCO (97 mg, 0.86 mmol). The mixture was stirred at 0° for 30 min then worked up as above to give 178 mg of 5e-(E) and (Z) as a 3:2 mixture. NMR (300 MHz, $CDCl_3$): δ8.16-8.01 (m,2); 7.90-7.61 (m,3); 7.43 (s,0.6); 7.04 (s,0.4); 1.55 and 1.47 (2 x s, 9).

Preparation of Bicyclic Pyrazolidinones 3 and 4. General Procedure.

Pyrazolidinone 13 (201 mg, 1 mmol) was slurried in 1,2-dichloroethane (5 ml), 37% aqueous formaldehyde (81 mg, 1 mmol) was added and the mixture stirred at room temperature until all of the pyrazolidinone dissolved (usually within 45 min). The solvent was removed in vacuo, the

residue taken up in 1,2-dichloroethane and reconcentrated to give a colorless foam. This residue was dissolved in 1,2-dichloroethane (5 ml), vinyl sulfone 5 (1 mmol) was added and the mixture refluxed for the time indicated. The mixture was cooled, N-methylmorpholine or DBU (1-2 eq) was added and, when elimination was complete, the resulting mixture was washed with 1N hydrochloric acid, saturated aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and concentrated in vacuo. The cycloadducts were isolated by flash chromatography or preparative HPLC.

Bicyclic pyrazolidinones 3a, 4a.

As above, pyrazolidinone 13 (60 mg, 0.3 mmol) was treated with 37% formaldehyde (24 mg, 0.3 mmol) followed by refluxing with vinyl sulfone 5a-(E) (98 mg, 0.28 mmol, 88% purity) in 1,2-dichloroethane (3.5 ml) for 1.5h. The mixture was cooled to -78°C, DBU (0.38 mmol) in CH_2Cl_2 (1 ml) was added and the mixture warmed to room temperature over 6h. Workup, followed by prep TLC (toluene/$CHCl_3$/MeOH 3:2:1) gave 50 mg (47%) of a 97:3 mixture of 3a:4a by HPLC and NMR comparison to authentic samples.[1c]

Bicyclic pyrazolidinone 3b.

As above, pyrazolidinone 13 (22.7g, 0.113 mol), pure (S)-isomer[11] was treated with 37% formaldehyde (10.1g, 0.125 mol) followed by refluxing with vinyl sulfone 5b-(E) (40g, 0.136 mol, 80% purity) in 1,2-dichloroethane (150 ml) for 1h. The mixture was cooled to room temperature, N-methylmorpholine (11.5g, 0.113 mol) was added and stirring continued overnight. Workup gave a 98:2 mixture of 3b:4b. Recrystallization from ethyl acetate/hexane (~2:1) afforded 25.3g of (S)-3b, m.p. 136-137°C, $\alpha]_{5461}^{25}$ -644° (C1,MeOH) identical by NMR, HPLC, and TLC with an authentic sample of (±) 3b.[1c] The product was found to be enantiomerically pure by deprotection (3N HCl/dry HOAc), acylation with Mosher's acid chloride[12] and determination of diastereomeric purity by NMR.

Bicyclic pyrazolidinones 3c,4c.

As above, pyrazolidinone 13, (201 mg, 1 mmol) was treated with 37% formaldehyde (97 mg, 1.19 mmol) followed by refluxing with vinyl sulfone 5c-(E) (410 mg, 1.45 mmol) in 1,2-dichloroethane (2 ml) for 2h. The mixture was cooled to -78°C, DBU (220 mg, 1.4 mmol) was added and the solution was allowed to warm to room temperature. Workup gave 240 mg of 3c:4c as a 98:2 mixture. Prep TLC (CH_2Cl_2:MeOH 8:2) gave 120 mg (32%) of pure 3c. NMR (90 MHz, $CDCl_3$): δ5.14 (bd,1,J=6); 4.7 (m,1); 4.32 (d,1,J=12.5); 4.0 (m,1); 3.84 (d,1,J=12.5); 2.80 (dd,1,J=8,11); 2.30 (s,3); 1.60 (s,9); 1.44 (s,9). UV λ_{max} (CH_3OH): 362 (ε 7,200). M.S.: Calcd. for $C_{18}H_{28}N_3O_6$(M+1): 382. 1979. Found: 382.1995 .

Pyrazolidinone 13 (96 mg, 0.45 mmol), 37% formaldehyde (40 mg, 0.5 mmol), sulfone 5c-(Z) (160 mg, 0.5 mmol) in 1,2-dichloroethane (2 ml) then DBU (64 mg, 0.42 mmol) gave 102 mg of crude product as a mixture of 3c:4c. Prep TLC (3:2:1 toluene, $CHCl_3$, MeOH) of 85 mg of this mixture gave primarily 4c, 40 mg (28%) as an oil. NMR (90 MHz, $CDCl_3$): δ5.12 (bd,1,J=6); 4.62 (m,1); 4.30 (d,1,J=11.6); 4.01 (m,1); 3.84 (d,1,J=11.6); 2.88 (dd,1,J=9,12); 2.53(s) and 2.27(s), ratio 95:5; 1.45 (s,18). UV λ_{max} (CH_3OH): 339 (ε 4,900).

Bicyclic pyrazolidinone 3d.

As above, pyrazolidinone 13 (428 mg, 2.13 mmol) was treated with 37% formaldehyde (172 mg, 2.13 mmol) followed by refluxing with vinyl sulfone 5d-(E) (0.75g, 2.13 mmol) in 1,2-dichloroethane (50 ml) for 6h. The mixture was cooled to room temperature, N-methyl morpholine (0.23 ml, 2.13 mmol) was added and stirring continued overnight. Workup, followed by flash chromatography on silica gel (40% EtOAc/hexanes) gave 0.34g (38%) of 3d as an orange oil. NMR (300 MHz, $CDCl_3$): δ5.98 (m,1); 5.29 (m,2); 5.10 (br s,1); 4.80 (m,3); 4.47 (d,1,J=12); 4.31 (m,2); 4.06 (d,1,J=12); 4.03 (m,1); 2.87 (t,1,J=9); 1.43 (s,9); 1.34 (t,3,J=8). UV (EtOH): λ_{max} = 392 (ε=2520). F.D.M.S.: M^+=423.

Bicyclic pyrazoldinone 3e.

As above, pyrazolidinone 13 (0.50g, 2.49 mmol) was treated with 37% formaldehyde (0.20g, 2.49 mmol) followed by refluxing with vinyl sulfone 5e-(E) (282 mg, 0.96 mmol) in 1,2-dichloroethane (20 ml) for 2 h. The mixture was cooled to room temperature, N-methylmorpholine (0.21 ml, 2 mmol) was added and stirring continued overnight. Workup, followed by flash chromatography on silica gel (1:1 EtOAc/hexanes) gave 154 mg (44%) of 3e as a yellow foam. NMR (300 MHz, $CDCl_3$): δ5.23 (brm,1); 4.74 (m,1); 4.34 (d,1,J=12); 4.08 (t,1,J=7);

3.92 (d,1,J=12); 2.92 (dd,1,J=9,12); 1.39 (s,9); 1.26 (s,9). IR ($CHCl_3$): 2230, 1746, 1725 cm^{-1}. UV (EtOH): λ_{max} = 360(ε=4518). F.D.M.S.: M^+=364.

Bicyclic pyrazoldinones 3e,4e.

As above, pyrazoldinone 13 (189 mg, 0.94 mmol) was treated with 37% formaldehyde (76 mg, 0.94 mmol) followed by refluxing with 5e-(E),(Z) (0.18g, 0.61 mmol, 3:2 mix) in 1,2-dichloroethane (10 ml) for 2h. The mixture was cooled to room temperature, N-methyl morpholine (0.21 ml, 2 mmol) was added and stirring continued overnight. Workup, followed by flash chromatography on silica gel (1:1 EtOAc/hexanes) gave 95 mg (43%) of 3e and 4e as an 86:14 mixture (NMR integration). NMR (300 MHz, $CDCl_3$): in addition to the resonances for 3e, signals appear at: δ4.44 (d,J=13); 2.99 (dd,J=9,13) and 4.08(t) is broadened.

Bicyclic pyrazoldinone 3f.

As above, pyrazolidinone 13 (1.81g, 9 mmol) was treated with 37% formaldehyde (729 mg, 9 mmol) followed by refluxing with vinyl sulfone 5f[6] (2.4g, 9 mmol) for 48h 1,2-dichloroethane (25 ml). The mixture was cooled, concentrated in vacuo and purified by flash chromatography on silica gel (gradient 0-50% EtOAc in hexanes) to give 2.17g of 6f as a mixture of diastereomers. NMR (270 MHz, $DMSOd_6$): δ7.90-7.80 (m,2); 7.58-7.46 (m,2); 5.82-5.56 (m,1); 5.28-5.12 (m,2); 4.87-4.68 (m,2); 4.66-4.28 (m,3); 3.85-3.74 (m,1); 3.66-3.46 (m,1); 3.40-3.26 (m,1); 3.20-2.96 (m,1); 2.88-2.72 (m,1); 2.55 (s,3); 1.39 (s,9). IR ($CHCl_3$): 1711 cm^{-1}. F.D.M.S.,: M^+=480. Cycloadduct 6f (100 mg, 0.209 mmol) was dissolved in dry CH_2Cl_2 (5 ml), cooled to -78°C and DBU (0.04g, 0.263 mmol) was added. The mixture was stirred at -78° for 1h then warmed slowly to room temperature. The mixture was washed with 0.1 N hydrochloric acid, saturated sodium bicarbonate, brine, dried ($MgSO_4$) and concentrated in vacuo to give 80mg (49% from 13) of 3f which was identical to previously reported material[1c].

References and Notes:

1. a. Jungheim, L.N.; Sigmund, S.K.; Fisher, J.W. Tetrahedron Lett. 1987, 28, 285. b.Jungheim, L.N.; Sigmund, S.K.; Jones, N.D.; Swartzendruber, J.K. ibid. 1987, 28, 289. c. Jungheim, L.N.; Sigmund, S.K. J. Org. Chem. 1987, 52, 4007.
2. Carr, R.C.V.; Williams, R.V.; Paquette, L.A. J. Org. Chem. 1983, 48, 4976.
3. a. Caramella, P.; Albini, E.; Bandiera, T.; Corsico Coda, A.; Grünanger, P.; Marinone Albini, F. Tetrahedron 1983, 39, 689. b. Barzaghi, M.; Beltrame, P.L.; Della Croce, P.; DelButtero, P.; Licandro, E.; Maiorana, S.; Zecchi, G. J. Org. Chem. 1983, 48, 3807. c. Shimizu, T.; Hayashi, Y.; Miki, M.; Teramura, K. ibid., 1985, 50, 904.
4. Boyd, D.B.; Foster, B.J.; Hatfield, L.D.; Hornback, W.J.; Jones, N.D.; Munroe, J.E.; and Swartzendruber, J.K. Tetrahedron Lett. 1986, 27, 3457. We thank these authors for sharing their results prior to publication and for providing us with samples of vinyl sulfoxides corresponding to 5a-(E) and 5c-(Z). Preliminary efforts to cycloadd these sulfoxides gave inferior results.
5. Larsson, E. J. Prakt. Chem. 1978, 320, 353. For examples confirmed by NOE experiments see: Nishida, A.; Shibasaki, M.; Ikegami, S. Chem. Pharm. Bull., 1986, 34, 1434.
6. Berdnikov, E.A.; Mukhitova, F.K.; Tantasheva, F.R.; Kataev, E.G. Zh. Org. Khim. 1977, 13, 1418. Allyl 2,3-dibromopropionate was prepared by esterification of 2,3-dibromopropionic acid (allyl alcohol, H_2SO_4). NMR (90 MHz, $CDCl_3$): δ7.76 (d,2,J=9); 7.34 (d,2,J=9); 7.32 (d,1,J=16); 6.78 (d,1,J=16); 6.12-5.68 (m,1); 5.42-5.17 (m,2); 4.66 (d,1,J=6); 2.43 (s,3).
7. For other cases of stereospecific elimination of β-substituted sulfones see Julia, M.; Uguen, D.: Righini, A.; Launay, M. and Verpeaux, J. in "Stereoselective Synthesis of Natural Products"; Bartmann, W.; Winterfeldt, E. Eds.; Elsevier North-Holland: New York, 1979; p. 163.
8. Bromination of 11b with bromine in the absence of triethylamine produced an unfavorable mixture of 5b-(E) and a product of dibromination of the methyl group of the acetyl moiety.
9. D. Neel, Lilly Research Laboratories, unpublished observations.
10. Paquette[2] has observed that cis-1-(phenylsulfonyl)-2-(trimethylsilyl) ethylene was less reactive towards cycloaddition with dienes than the trans isomer.
11. Jungheim, L.N.; Holmes, R.E. "4-Substituted Diazolidinones." Eur. Pat. Appl. 202,795, 11/26/86; U.S. Appl. 728,734, 4/30/85.
12. Dale, J.A.; Dull, D.L.; Mosher, H.S. J. Org. Chem. 1969, 34, 2543.
13. The C-3 cyano nucleus was first prepared by a regiochemically unambiguous route. Acylated analogs of 3e have been prepared and were found to exhibit greater antibacterial potency than LY186826. R.J. Ternansky, Lilly Research Laboratories, unpublished results.
14. Otto, R.; Otto, W. J. Prakt. Chem. 1887, 36(2), 403.
15. Banfield, J.E.; Davies, W.; Gamble, N.W.; Middleton, S. J. Chem. Soc. 1956, 4791.
16. The preparation of the pure stereoisomers of 5c may be conveniently carried out via silica flash chromatography (CH_2Cl_2 elution) of the corresponding sulfoxides (method of J.E. Munroe and W.J. Hornback, reference 4), followed by peracid oxidation to the sulfones.
17. Andreichikov, Y.S.; Fridman, A.L.; Gein, V.L.; Gein, L.F. Zh. Org. Khim. 1977, 13, 2070.