J. Org. Chem. 1987, 52, 4007-4013

1,3-Dipolar Cycloaddition Reactions of Pyrazolidinium Ylides with Acetylenes. Synthesis of a New Class of Antibacterial Agents

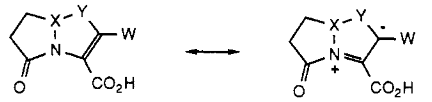
Louis N. Jungheim* and Sandra K. Sigmund

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

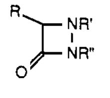
Received April 15, 1987

In an effort to prepare biologically active γ-lactam analogues of β-lactam antibiotics we prepared bicyclic pyrazolidinone LY173013. The exciting antibacterial activity of this prototype compound has prompted us to search for more potent analogues. A series of bicyclic pyrazolidinone nuclei **10** were prepared via a 1,3-dipolar cycloaddition reaction of pyrazolidinium ylide **8** and a variety of 3-substituted propiolate esters. Conditions for the in situ generation of ylide **8** from pyrazolidinone **7** and formaldehyde are described. Trapping of this ylide with unsymmetrical acetylenic esters typically gave mixtures of regioisomeric cycloadducts **10** and **11**. However, in select cases excellent regioselectivity was observed. Acylation of bicyclic pyrazolidinone **10d** with a typical β-lactam side chain gave LY186826, which exhibits significantly increased antibacterial potency relative to LY173013.

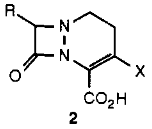
Since the 1940s attempts to prepare biologically active γ-lactam analogues of β-lactam antibiotics have been undertaken.[1] Until recently none of these compounds had shown significant antibacterial or β-lactamase inhibitory activity.[2] For some time now we have been interested in preparing γ-lactam analogues of several of the more recently discovered classes of β-lactams. β-Lactams are known to exert their activity by acylation of several specific enzymes, the penicillin binding proteins (PBP's), involved in bacterial cell wall biosynthesis.[3] We reasoned that a suitably activated γ-lactam could also operate via this mechanism. By analogy to the cephalosporins, we hypothesized that electron-withdrawing groups (W) at C-3 of a bicyclic γ-lactam would heighten the reactivity of the amide bond by delocalization of the amide nitrogen's lone pair of electrons away from the amide carbonyl group.[4,5] In addition, the incorporation of a classical acylamino side chain at C-7 should offer the best opportunity to observe biological activity. The recent reports of Morin,[6] Munroe,[7] and Baldwin,[8] disclosing biologically active γ-lactam analogues of the penems and carbapenems, lend support to this hypothesis.



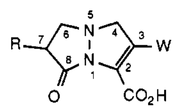
A third type of highly reactive β-lactam is the aza-β-lactam **1** recently described by Taylor.[9] These compounds have proven to be especially unstable and attempts to prepare suitably elaborated bicyclic analogues, e.g., **2**, have failed. The increased unstability of the aza-β-lactams relative to the corresponding azetidinones suggested that a pyrazolidinone homologue, e.g., **3**, might provide the proper mixture of chemical stability and acylating ability to exhibit antibacterial activity.



1

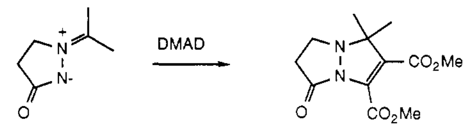


2

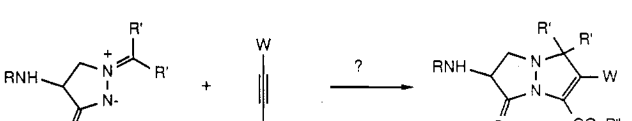


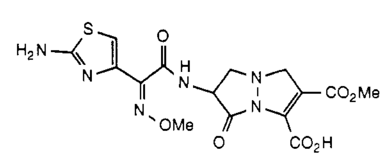
3

In designing a synthetic approach to such pyrazolidinones our attention was drawn to a report by Dorn[10] of the 1,3-dipolar cycloaddition of pyrazolidinium ylide **4** with dimethyl acetylenedicarboxylate. The ready availability of this simple bicyclic pyrazolidinone **5** prompted us to



4 5





LY173013

---

[1] Du Vigneaud, V.; Carpenter, F. H. In *The Chemistry of Penicillin*; Clarke, H. T., Johnson, J. R., Robinson, R., Eds.; Princeton Univeristy Press: Princeton, NJ, 1949; p 1004. Wasserman, H. H.; Precopio, F. M.; Liu, T. C. *J. Am. Chem. Soc.* **1952**, *74*, 4093. Wasserman, H. H.; Suryanarayana, B.; Koch, R. C.; Tse, R. L. *Chem. Ind.* (*London*) **1956**, 1022. Todd, D.; Teich, S. *J. Am. Chem. Soc.* **1953**, *75*, 1895. Gordon, E. M.; Pluscec, J. *Tetrahedron Lett.* **1983**, *24*, 3419. Baldwin, J. E.; Chan, M. F.; Gallacher, G.; Monk, P.; Prout, K. *J. Chem. Soc., Chem. Commun.* **1983**, 250. Baldwin, J. E.; Chan, M. F.; Gallacher, G.; Otsuka, M.; Monk, P.; Prout, K. *Tetrahedron* **1984**, *40*, 4513. Baldwin, J. E.; Adlington, R. M.; Jones, R. H.; Schofield, C. J.; Zarocostas, C.; Greengrass, C. W. *J. Chem. Soc., Chem. Commun.* **1985**, 194.

[2] During the course of this investigation a U.S. patent appeared disclosing 2-oxo-3-amino-6-(substituted-thio)-1-azabicyclo[3.2.0]hept-6-ene-7-carboxylic acids as antibiotic substances: U.S. Pat. 4428960, 1984; *Chem. Abstr.* **1984**, *100* (23), 191655.

[3] Waxman, D. J.; Strominger, J. L. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 3, p 209.

[4] Boyd, D. B. In *The Chemistry & Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 1, pp 437–545.

[5] We have adopted this numbering system so "activating" substituents reside at C-3 with acylamino side chains at C-7, as they do in a cephalosporin nucleus.

[6] Boyd, D. B.; Elzey, T. K.; Hatfield, L. D.; Kinnick, M. D.; Morin, J. M. *Tetrahedron Lett.* **1986**, *27*, 3453.

[7] Boyd, D. B.; Foster, B. J.; Hatfield, L. D.; Hornback, W. J.; Jones, N. D.; Munroe, J. E.; Swartzentdruber, J. K. *Tetrahedron Lett.* **1986**, *27*, 3457.

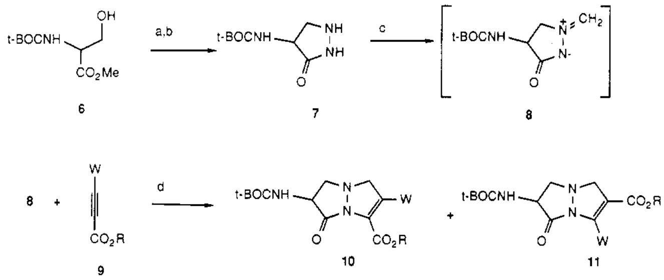
[8] Baldwin, J. E.; Lowe, C.; Schofield, C. J.; Lee, E. *Tetrahedron Lett.* **1986**, *27*, 3461.

[9] Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 7743. Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113. Taylor, E. C.; Davies, H. M. L. *Ibid.* **1984**, *49*, 4415. Also see: Moody, C. J.; Pearson, C. J.; Lauton, G. *Tetrahedron Lett.* **1985**, *26*, 3167.

[10] Dorn, H.; Otto, A. *Chem. Ber.* **1968**, *101*, 3287. Attempts to prepare the corresponding bis acid by basic hydrolysis of **5** lead to the decomposition of the bicyclic pyrazolidinone ring system.

0022-3263/87/1952-4007$01.50/0 © 1987 American Chemical Society

Scheme I[a]



[a] (a) TsCl, pyridine; (b) N_2H_4, CH_2Cl_2; (c) aqueous H_2CO, $EtCl_2$; (d) $EtCl_2$ or CH_3CN, reflux.

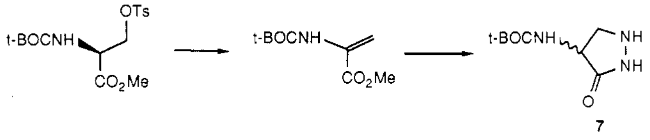
pursue a similar approach to our target compounds.

In a preliminary report we have reported that bicyclic pyrazolidinone LY173013 possesses broad spectrum antibacterial activity against a variety of gram-positive and gram-negative bacteria.[11] The search for more potent analogues has prompted us to explore the scope of the 1,3-dipolar cycloaddition reaction which provided ready access to the nucleus of LY173013. Indeed, we have found that a wide variety of bicyclic pyrazolidinones can be obtained from the 1,3-dipolar cycloaddition of pyrazolidinium ylides with various propiolate esters. These findings are the topic of this report.

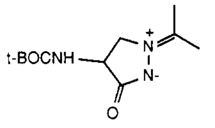
Results and Discussion

The chemistry of pyrazolidinium ylides derived from the reaction of pyrazolidinones with ketones or aromatic aldehydes has been well-studied.[12] In order to more closely mimic the structure of a β-lactam, we desired to prepare bicyclic pyrazolidinones unsubstituted at C-4.[13] Thus, we needed to generate an unsubstituted ylide (8) which in theory is available from pyrazolidinone 7 and formaldehyde (Scheme I). Previous attempts to generate closely related azomethine imines have resulted in the formation of dimeric species in low yield.[14] No attempts to trap any intermediate ylide with a dipolarophile were reported. Oppolzer[15] has shown that certain *N*-acyl-*N′*-alkylhydrazines react with formaldehyde to generate azomethine imines as reactive intermediates. Once generated, these ylides have been trapped with several dipolarophiles. These results supported the feasibility of generating ylide 8 and trapping it in situ with a variety of acetylenes.

The required 4-[[(*tert*-butyloxy)carbonyl]amino]pyrazolidin-3-one (7) is readily available from D,L-serine. Tosylation of 6 followed by treatment with anhydrous hydrazine gave the desired pyrazolidinone 7 in 60% yield. The use of L-serine also gave rise to racemic 7 by this procedure. Initially we thought the racemization was the result of hydrazine-catalyzed elimination of tosylate to give the dehydro amino ester. However, when the dehydro amino ester was treated with hydrazine under the normal reaction conditions, only poor yields of 7 could be obtained. It seems more likely that the pyrazolidinone itself or one of several possible intermediates is suffering base-catalyzed racemization. The choice of *t*-BOC and tosylate groups was found to be critical for the efficient production of the desired pyrazolidinone.



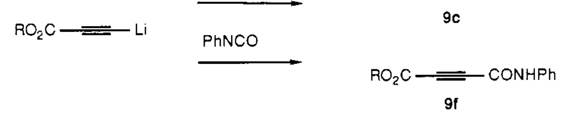
At this point, we were ready to explore the feasibility of generating the unsubstituted ylide 8. Addition of 37% aqueous formaldehyde to a slurry of 7 in 1,2-dichloroethane resulted in the gradual dissolution of the pyrazolidinone and its disappearance as judged by TLC analysis. Removal of the solvent in vacuo gave rise to a white amorphous solid which could not be fully characterized. Evidence for the desired ylide 8 ($M^+ = 213$ strong) as well as a dimeric form ($M^+ = 426$ weak) was evident in the field desorption mass spectrum. There was no absorption in the UV spectrum at wavelengths greater than 210 nm in contrast to the stable acetone derived ylide 12 which exhibits a λ_{max} 267 nm. Severe line broadening was evident in the NMR spectrum. Identical results were obtained when a stream of dry formaldehyde gas was bubbled through a slurry or solution of 7 in solvents such as methanol or acetonitrile. Paraformaldehyde was not reactive. Nevertheless, heating this amorphous material to reflux in either 1,2-dichloroethane or acetonitrile in the presence of dimethyl acetylenedicarboxylate provided the desired cycloadduct **10a** in 88% yield! This product is at least formally derived from the 1,3-dipolar cycloaddition of ylide 8 and DMAD.



12

We wanted to prepare a series of bicyclic pyrazolidinones variously substituted at C-3 to observe the substituent effect on antibacterial spectrum and potency (vide supra). Thus, we explored the scope of this cycloaddition reaction. We found that the synthetic utility of this approach is dependent on several factors: (1) The availability of 3-substituted propiolic esters. (2) The ability of these acetylenes to engage in this cycloaddition. (3) Whether or not the cycloaddition would proceed in the desired regiochemical sense.

Many of the acetylenic esters 9 employed in this study were prepared via modified literature procedures. The lability of the bicyclic pyrazolidinones to basic hydrolysis (vide infra) necessitated the use of allyl or *tert*-butyl esters, which can be hydrolyzed under neutral or acidic conditions. Allyl methyl acetylenedicarboxylate (**9c**) was most conveniently prepared by reaction of allyl 3-lithiopropiolate with methyl chloroformate. Likewise, carboxamido-substituted propiolate **9f** was obtained by quenching *tert*-butyl 3-lithiopropiolate with phenyl isocyanate.



Our in situ generated ylide 8 was found to react with a variety of 3-substituted propiolate esters. The results are summarized in Table I. Not unexpectedly, mixtures of regioisomeric products were often obtained. In several

---

[11] (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.

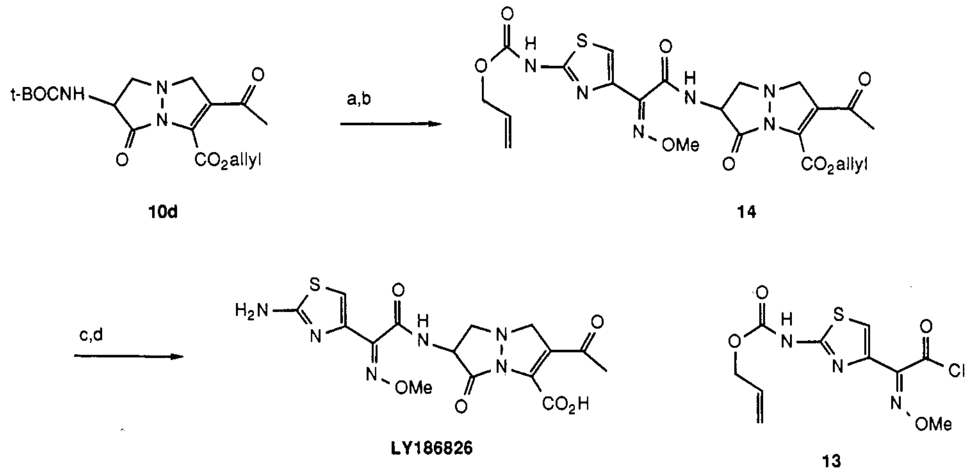
[12] Grashey, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, p 733.

[13] We have found that optimum antibacterial activity is obtained with compounds that are unsubstituted at C-4 of the bicyclic pyrazolidinone nucleus.

[14] Dorn, H.; Zubek, A. *Z. Chem.* **1968**, *7*, 270. Dorn, H.; Ozegowski, R.; Radeglia, R. *J. Prakt. Chem.* **1977**, *319*, 177. Taylor, E. C.; Clemens, R. J.; Davies, H. M. L. *J. Org. Chem.* **1983**, *48*, 4567.

[15] Oppolzer, W. *Tetrahedron Lett.* **1970**, 2199. For an intramolecular version of this cycloaddition reaction, see: Jacobi, P. A.; Brownstein, A.; Martinelli, M.; Grozinger, K. *J. Am. Chem. Soc.* **1981**, *103*, 239.

Scheme II[a]



[a] A 1:1 mixture of **10d** and **11d** was utilized in this scheme. Only the desired regioisomer is shown for clarity. (a) TFA, 5 min; (b) BSTFA, THF then **13** in EtOAc; (c) $[Ph_3P]_4Pd$, n-Bu_3SnH, acetone, then HCl; (d) C_{18} chromatography.

Table I. Cycloaddition of Ylide 8 with Acetylenic Esters 9

acetylene	W	R	time, h	ratio[a] 10:11	yield,[b] %
9a	CO_2Me	Me	4	10 ≡ 11	88
9b	CO_2allyl	allyl	3	10 ≡ 11	33
9c	CO_2Me	allyl	4	1:1	38
9d	COMe	allyl	4	2:3	26
9e	COPh	allyl	6	1:4	29
9f	CONHPh	t-Bu	6	1:1	25
9g	PO_3Me_2	allyl	2.5	1:0	46
9h	CF_3	t-Bu	21	1:0	9[c]
9i	CH_2OTHP	allyl	40	0:1	10[d]
9j	CH_2OH	allyl	18	2:3	28
9k	H	allyl	16	1:0	23
9l	Ph	allyl	8	0:1	10
9m	SPh	allyl	18	0:1	24

[a] Determined by NMR integration of the crude reaction mixture. [b] Yield of purified cycloadducts based on amount of acetylene consumed. Yields are unoptimized except for dimethyl acetylenedicarboxylate. [c] Yield of purified cycloadduct based on amount of pyrazolidinone **7** consumed. [d] A 6% yield of **11j** was also isolated from the reaction mixture.

instances only a single regioisomer was obtained; however, yields tended to be low. Examination of the crude reaction mixtures by NMR provided no evidence for the formation of the other regioisomer in these cases.

It is evident from the data in Table I that propiolate esters substituted with an additional electron-withdrawing group are most likely to give reasonable yields of the desired regioisomer **10**. Two notable exceptions are allyl propiolate,[16] giving only **10k**, and allyl 4-hydroxy-2-butynoate (**9j**), giving a mixture of **10j** and **11j**. The latter result is in striking contrast to the THP-protected analogue **9i**, which provides only isomer **11i** in low yield.

The regioisomers were typically separable by flash chromatography or preparative HPLC. Isolation of the cycloadducts was frequently simplified by the fact that most of these bicyclic pyrazolidinones are bright yellow. We attribute this to their characteristically broad absorption band in the UV with λ_{max} ≥335 nm.

Assignment of regiochemistry of **10** vs. **11** was made on the basis of the following observations. The structures of **10c**, **10d**, and **11e** were determined by X-ray crystallography.[17] In each cycloadduct which unambiguously bears an ester substituent at C-3 (e.g., **10a–c** and **11d,e**), the UV spectrum exhibited a λ_{max} ≥335 nm. All compounds with a carbonyl group at C-3 exhibit UV: λ_{max} ≥330 nm. Compounds with substituents other than a carbonyl moiety at C-3 typically absorb between 280 and 320 nm. For example: **10j** exhibits λ_{max} 283 nm while the regioisomeric **11j** exhibits λ_{max} 335 nm. Furthermore, the NMR chemical shifts observed for the substituents at C-2 and C-3 displayed a useful trend. The observed resonance for a substituent at C-2 tends to be shifted ca. 0.2–0.3 ppm downfield from the signal corresponding to the same substituent residing at C-3. For example, the methyl ester resonance of **10c** appears at δ 3.66 and at δ 3.84 in the regioisomeric **11c**. The methyl ketone resonances of **10d** and **11d** appear at δ 2.25 and 2.52, respectively. Similar chemical shift trends are observed for all pairs of regioisomers in Table I. These chemical shift correlations as well as the UV spectral data have allowed the assignment of regiochemistry when only a single regioisomer is obtained.

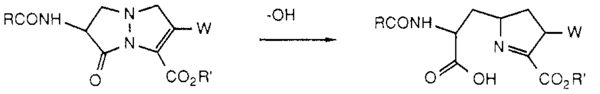
It remained for us to append an appropriate cephalosporin side chain at C-7 and remove any protecting groups. We have found these compounds to be quite sensitive to ester hydrolysis conditions. Treatment with hydroxide ion, for example, at pH 10 results in rapid and selective hydrolysis of the lactam linkage.[18] This observation is im-

---

(16) Reaction of ylide **4** with allyl propiolate gave only the C-3 ester substituted regioisomer, corresponding to structure **11**, in 67% yield.

(17) For the structure of **10c** see ref 11b. X-ray crystallography was performed by Dr. Noel Jones, John Swartzendruber, and Jack Deeter of Lilly Research Laboratories. Compound **10d** crystallized from hexane/ethyl acetate in the space group $P\bar{1}$, $Z = 2$, with unit cell dimensions of $a = 5.211$ (2) Å, $b = 13.114$ (8) Å, $c = 14.990$ (7) Å, $\alpha = 106.857$ (4)°, $\beta = 93.005$ (4)°, $\gamma = 100.154$ (4)°. The calculated density was 1.27 g cm^{-3}. A total of 2608 unique reflections with $2\theta < 116.0$ were measured on an automated four-circle diffractometer using monochromatic copper radiation. The structure was solved by using the direct method routine SOLV of the SHELXTL program library (G. M. Sheldrick, 1981) and was refined by the least-squares method with anisotropic temperature factors for all atoms except hydrogen. Hydrogen atoms were included with isotropic temperature factors at calculated positions. The final R factor was 0.0898 for 1872 observed reflections. Compound **11e** crystallized from hexane/ethyl acetate as yellow prisms in the space group $P\bar{1}$, $Z = 2$, with unit cell dimensions of $a = 9.700$ Å, $b = 11.984$ Å, $c = 9.959$ Å, $\alpha = 96.655$, $\beta = 114.379$, $\gamma = 99.174$. The calculated density was 1.265 g cm^{-3}. A total of 3055 unique reflections with $2\theta < 116.0$ were measured on an automated four-circule diffractometer using monochromatic copper radiation. The structure was solved by using the random tangent routine RANT of the SHELXTL program library (G. M. Sheldrick, 1981) and was refined by the least-squares method with anisotropic temperature factors for all atoms except hydrogen. Hydrogen atoms were included with isotropic temperature factors at calculated positions. The final R factor was 0.0578 for 2253 observed reflections.

(18) Indelicato, J. M.; Pasini, C. E. *The Acylating Potential of Gamma-Lactam Antibacterials: The Base Hydroysis of Bicyclic Pyrazolidinones*; Abstract #602, XXVI Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 1986.



portant in that it was our goal to prepare a five-membered ring lactam with enhanced chemical reactivity, while retaining chemical stability. It also supports the hypothesis that these compounds might mimic a β-lactam, with regards to their biological mode of action.

The conversion of **10d** into LY186826 is illustrative of the transformations required to convert these bicyclic pyrazolidinones into fully elaborated antibacterial agents (Scheme II). A 1:1 mixture of **10d** and **11d** was treated with trifluoroacetic acid to remove the *t*-BOC protecting group. The resulting amine was treated with the acid chloride of [2-[[(allyloxy)carbonyl]amino]thiazol-4-yl]-(methoxyimino)acetic acid (**13**) in the presence of *N*,*O*-bis(trimethylsilyl)trifluoroacetamide, as an acid scavenger, to give the desired acylation products **14**. The use of the allyloxycarbonyl (Aloc) protecting group on the side chain is noteworthy. N-Trityl or N-formyl groups are most typically employed to protect the aminothiazole side chain. The conditions required for their removal (strong acid) often resulted in severe decomposition of the acylated pyrazolidinones. By employing the Aloc group in conjunction with an allyl ester we hoped to remove both remaining protecting groups in one step. In practice, palladium(0)-catalyzed cleavage[19] of the allyl ester and Aloc moieties in the presence of tri-*n*-butyltin hydride efficiently provided the desired amino acids. Finally these regioisomers were separated by reverse-phase preparative liquid chromatography to give pure LY186826.

While most of the bicyclic compounds in Table I have been similarly elaborated, LY186826 was uniquely found to be significantly more potent than our initial lead compound LY173013.[20]

In summary we have developed a useful procedure for the in situ generation of unsubstituted pyrazolidinium ylide **8**. This intermediate can be trapped by a variety of substituted acetylenic esters, giving rise to bicyclic pyrazolidinones. In select cases only a single regioisomer was obtained from these 1,3-dipolar cycloaddition reactions. Unfortunately this approach suffers from a general lack of regiocontrol. Our efforts to circumvent this problem will be the subject of a future report. The cycloadducts obtained in this reaction represent the nuclei of an exciting new class of synthetic antibacterial agents. Recent studies with LY186826 indicate that it is indeed a bacterial cell wall synthesis inhibitor which acts on β-lactam target enzymes.[21] In general these compounds appear to be quite stable to β-lactamases and they treat infections in animal models.[22] A complete discussion of the biological properties of these unique antibacterial agents will be published in due course.

Experimental Section

General Procedure. All reactions were run under a positive pressure of dry nitrogen or argon. The NMR spectra were obtained on a Varian Associates EM-390 90-MHz or T-60 60-MHz instrument, on a JEOL FX-90Q 90-MHz instrument, on a Brüker Corp. 270-MHz instrument, or on a General Electric QE-300 300-MHz instrument. The chemical shifts are expressed in δ values (parts per million downfield from tetramethylsilane). In conjunction with the NMR spectra, the following abbreviations are used: s is singlet, d is doublet, dd is doublet of doublets, t is triplet, q is quartet, m is multiplet, dm is a doublet of multiplets, and br s, br d, and br t are broad singlet, doublet, and triplet, respectively. *J* indicates the coupling constant in hertz. The field desorption mass spectra (FDMS) in *m*/*e* were taken on a Varian-MAT 731 spectrometer using carbon dendrite emitters. Electron impact mass spectra were obtained on a CEC 21-110 instrument from Consolidated Electrodynamics Corporation. Infrared spectra were obtained on a Perkin-Elmer 281 instrument. Ultraviolet spectra were obtained on a Cary 118 instrument. Flash chromatography was carried out on E. Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography was carried out on E. Merck silica gel plates. Preparative HPLC was performed on a Waters Prep 500 system. Melting points are uncorrected.

In experiments requiring dry solvents, tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl.

Preparation of 4-[(*tert*-Butoxycarbonyl)amino]-pyrazolidin-3-one (7). Methyl 3-hydroxy-2(*S*)-[(*tert*-butoxycarbonyl)amino]propionate (**6**) (58 g, 196 mmol), methylene chloride (150 mL), *p*-toluenesulfonyl chloride (43.35 g, 227.4 mmol), 4-(dimethylamino)pyridine (2.4 g, 19.6 mmol), and pyridine (30 mL, 371 mmol) were combined and stirred at room temperature overnight. The reaction solution was concentrated in vacuo to a pale yellow oil. The oil was stored in vacuo overnight; then the white solid that formed was isolated to give 75.33 g of crude product. The product was triturated in petroleum ether (approximately 200 mL) to yield the tosylate. NMR ($CDCl_3$, 90 MHz): δ 7.72, 7.31 (2 × dd, 4, aromatic protons), 5.26 (m, 1, nitrogen proton), 4.48 (m, 1, C-2 proton), 4.32 (m, 2, C-3 protons), 3.68 (s, 3, methyl protons of methyl ester), 2.44 (s, 3, methyl protons of toluene moiety), 1.40 (s, 9, protons of *t*-Bu moiety). IR ($CHCl_3$): 3435, 3019, 1753, 1711, 1502, 1369, 1351, cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_7S$: C, 51.19; H, 6.71; N, 3.73; S, 8.54. Found: C, 51.05; H, 6.50; N, 3.63; S, 8.13. Under a nitrogen atmosphere, methylene chloride (50 mL) was cooled in an ice bath and anhydrous hydrazine (97%, 11.0 g, 333 mmol) was added. The ice bath was removed and the solution was stirred until it warmed to room temperature. At this time a solution of the above prepared tosylate (20.0 g, 53.6 mmol) in methylene chloride (50 mL) was gradually added. The reaction solution was stirred under nitrogen at room temperature for 5 h. The solution was then concentrated under reduced pressure and the concentrate was taken up in saturated aqueous sodium bicarbonate solution. The aqueous solution was continuously extracted for 14 h with methylene chloride (700 mL). The methylene chloride solution was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 5.15 g, 48%, of pyrazolidinone **7** as a white powder. Yields up to 60% can be obtained by extending the time of continuous extraction. NMR ($CDCl_3$, 90 MHz): δ 7.04 (m, 1), 5.12 (m, 1), 4.28 (m, 1, C-4 proton), 3.94 (m, 1, C-5 proton), 3.20 (m, 1, C-5 proton), 1.45 (s, 9, *t*-Bu protons). IR ($CHCl_3$): 3430, 3019, 1702, 1545, 1503 cm^{-1}. FDMS: M$^+$ 201. Anal. Calcd for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51; N, 20.88. Found: C, 47.80; H, 7.56; N, 20.61.

Preparation of 4(*RS*)-[(*tert*-Butoxycarbonyl)amino]-3-oxo-1-(dimethylmethylene)-1,2-pyrazolidinium Ylide (12). Pyrazolidinone 7 (2.01 g, 10 mmol) was dissolved in methanol (20 mL). To this solution was added acetone dimethyl acetal (10 mmol) and *d*-10-camphorsulfonic acid (approximately 5 mg). The mixture was refluxed for 1.5 h and then concentrated in vacuo. The concentrate was recrystallized from dichloromethane/isopropyl ether to give 2.01 g of 4-(*R*,*S*)-[(*tert*-butoxycarbonyl)-amino]-3-oxo-1-(dimethylmethylene)-1,2-pyrazolidinium ylide (**12**).

---

[19] Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.

[20] Jungheim, L. N.; Holmes, R. E.; Ott, J. L.; Ternansky, R. J.; Draheim, S. E.; Neel, D. A.; Shepherd, T. A.; Sigmund, S. K. *Bicyclic Pyrazolidinones, Synthesis and In Vitro Activity of a New Class of Synthetic Antibacterial Agents*; Abstract #601, XXVI Interscience Conference on Antimicrobial Agents and Chemitherapy (ICAAC), 1986. For example, MICs (μg/mL) of LY173013 vs. *Streptococcus pyogenes* = 4; *Providencia rettgeri* = 1; and for LY186826 vs. *S. pyogenes* = 0.5; *P. rettgeri* = 0.25.

[21] Hobbs, J. N., Jr.; Andonov-Roland, M. M.; Allen, N. E. *Inhibition of Peptidoglycan Biosynthesis by LY186826*; Abstract #604, XXVI Interscience Conference on Antimicrobial Agents and Chemitherapy (ICAAC), 1986.

[22] Preston, D. A.; Counter, F. T.; Felty-Duckworth, A. M.; Turner, J. R. *Some Interesting Biological Properties of LY173013 and LY186826, Two Bicyclic Pyrazolidinones*; Abstract #603, XXVI Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 1986.

NMR (270 MHz, DMSO-d_6): δ 7.2 (d, 1, J = 6), 4.54 (t, 1, J = 10), 4.28 (m, 1), 3.85 (m, 1), 2.25 (s, 3), 2.18 (s, 3), 1.4 (s, 9). IR (KBr): 3232, 1692, 1671, 1608 cm^{-1}. MS: M$^+$ 241. UV (EtOH): λ_{max} 267 (ϵ 19620).

Preparation of Allyl Methyl Acetylenedicarboxylate (9c). To a −78 °C solution of hexamethyldisilazane (56.7 mL, 0.263 mol) in dry THF (500 mL) was added a solution of n-BuLi in hexane (165 mL, 0.263 mol, 1.6 M). After 30 min at −78 °C, a solution of allyl propiolate (29.0 g, 0.263 mol) in THF (100 mL, precooled to −78 °C) was added dropwise. The resulting solution was stirred for 30 min and then transferred via cannula to a −78 °C solution of methyl chloroformate (50 mL, 0.65 mol) in THF (100 mL). After 1 h the cooling bath was removed and the mixture allowed to warm to 0 °C. Saturated aqueous ammonium chloride solution (250 mL) was added and this mixture was extracted with ether (3 × 250 mL). The combined organic extracts were washed with 1 N hydrochloric acid (3 × 100 mL), saturated aqueous sodium bicarbonate solution (100 mL), and brine. The extracts were dried (Na_2SO_4) and concentrated in vacuo below room temperature. The residue was purified via Kugelrohr distillation, collecting the fraction boiling at 60–75 °C (bath temperature) (4 mmHg) to give 8.33 g (19%) of acetylene **9c** as a colorless oil. NMR (90 MHz, $CDCl_3$): δ 6.2–5.7 (m, 1), 5.5–5.16 (m, 2), 4.72 (dm, 2, J = 6), 3.84 (s, 3). IR ($CHCl_3$): 1725 cm^{-1}. Anal. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.28; H, 4.76.

Preparation of Allyl 4-Oxopentynoate (9d). Using the method of Midland et al.,[23] the lithium salt of allyl propiolate (0.24 mol) and freshly distilled acetaldehyde (0.25 mol) were condensed, followed by Jones oxidation to give after Kugelrohr distillation, 9.65 g (31%) of allyl 4-oxopentynoate, bp 60–100 °C (bath temperature) (4 mmHg). NMR (90 MHz, $CDCl_3$): δ 6.12–5.7 (m, 1), 5.48–5.12 (m, 2), 4.68 (dm, 2, J = 6), 2.38 (s, 3). IR ($CHCl_3$): 1720, 1687 cm^{-1}. MS: M$^+$ 152.

Preparation of Allyl 4-Oxo-4-phenylbutynoate (9e). Using the method of Midland et al.,[23] the lithium salt of allyl propiolate (0.12 mol) and benzaldehyde (0.14 mol) were condensed, followed by Jones oxidation to give after Kugelrohr distillation, 18.4 g (87%) of allyl 4-oxo-4-phenylbutynoate, bp 85–110 °C (bath temperature) (0.4 mmHg). NMR (90 MHz, $CDCl_3$): δ 8.06 (m, 2), 7.7–7.32 (m, 3), 6.16–5.7 (m, 1), 5.5–5.2 (m, 2), 4.72 (dm, 2, J = 6).

Preparation of *tert*-Butyl 3-(Phenylcarbamoyl)propiolate (9f). *tert*-Butyl propiolate (3.78 g, 30 mmol) was dissolved in THF and cooled to −78 °C. A hexane solution of n-butyllithium (1.5 m, 20 mL, 30 mmol) was added and the solution was stirred at −78 °C for 30 min. Phenyl isocyanate (3.25 mL, 30 mmol) was added and the solution was stirred for 10 min at −78 °C. The cooling bath was removed and the reaction was quenched with saturated aqueous ammonium chloride solution. The solution was warmed to room temperature, diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution, water, and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give an oil. The oil was flash chromatographed on silica gel eluted with a gradient of 10% ethyl acetate/hexane to 15% ethyl acetate/hexane to give 5.0 g, 68% yield of acetylene **9f**. NMR (90 MHz, $CDCl_3$): δ 8.10 (br s, 1), 7.7–7.1 (m, 5), 1.60 (s, 9). IR ($CHCl_3$): 1710, 1675 cm^{-1}. MS: M$^+$ 245.

Preparation of Allyl (Dimethoxyphosphinyl)propynoate (9g). Using the method of Trippett,[24] trimethyl phosphite (0.1 mol) and allyl (Z)-2,3-dibromopropionate[25] (0.099 mol) gave allyl 2-bromo-3-dimethylpropenyl phosphonate. The phosphonate (50 mmol) in ether (200 mL) was cooled to −78 °C and treated with DBU (52.5 mmol). After 15 min the cooling bath was removed and the mixture warmed to room temperature. The supernatant liquid was decanted and the gummy residue was triturated several times with ether. The combined ether extracts were concentrated in vacuo to give a brown oil which was purified by flash chromatography, eluting with 1:1 hexane/ethyl acetate, to give 1.74 g (16%) of the desired allyl (dimethoxyphosphinyl)propynoate. NMR (60 MHz, $CDCl_3$): δ 6.4–5.7 (m, 1), 5.6–5.2 (m, 2), 4.75 (d, 2, J = 6), 3.9 (d, 6, J = 13). IR ($CHCl_3$): 1723, 1273, 1235, 1045 cm^{-1}. Anal. Calcd for $C_8H_{11}O_5P$: 44.05; H, 5.08; P, 14.20. Found: C, 43.99; H, 5.22; P, 13.97.

Preparation of Allyl γ-[(Tetrahydropyran-2-yl)oxy]tetrolate (9i). Using the method of Warrener[26] tetrahydro-2-(2-propynyloxy)-2H-pyran (0.156 mol) and allyl chloroformate (0.165 mol) were condensed to give after flash chromatography (15% ethyl acetate/hexane) 31.3 g (89%) of the desired acetylene **9i** as a colorless oil. NMR (90 MHz, $CDCl_3$): δ 6.12–5.70 (m, 1), 5.44–5.16 (m, 2), 4.78 (m, 1), 4.64 (dm, 2, J = 6), 4.34 (s, 2), 3.9–3.4 (m, 2), 1.9–1.4 (m, 6). IR ($CHCl_3$): 2245, 1714 cm^{-1}. FDMS: M$^+$ 224.

Preparation of Allyl γ-Hydroxytetrolate (9j). Tetrahydropyranyl ether **9i** (76.9 mmol) was hydrolyzed[26] to give after flash chromatography (1:1 hexane/ethyl acetate) 5.04 g (47%) of the desired alcohol **9j**, which contained a small impurity by NMR. NMR (90 MHz, $CDCl_3$): δ 6.1–5.64 (m, 1), 5.5–5.12 (m, 2), 4.62 (dm, 2, J = 6), 4.35 (d, 2, J = 7), 2.2 (br s, 1).

Preparation of Allyl 3-(Phenylthio)propiolate (9m). Using the method of Schultz,[27] the lithium salt of allyl propiolate (40 mmol) was condensed with phenyl (phenylthio)sulfonate (80 mmol) to give 7.41 g (85%) of allyl 3-(phenylthio)propiolate as a yellowish tinted oil. Attempted distillation of a small portion of this material resulted in decomposition. NMR (90 MHz, $CDCl_3$): δ 7.40 (m, 5), 6.2–5.7 (m, 1), 5.5–5.2 (m, 2), 4.68 (dm, 2, J = 6).

Preparation of Bicyclic Pyrazolidinones. General Procedure. Reaction of Pyrazolidinone 7 with Formaldehyde. Pyrazolidinone **7** (4.02 g, 20 mmol) was slurried in 1,2-dichloroethane (80 mL). Aqueous formaldehyde (37%) (1.62 g, 20 mmol) was added, and the mixture was stirred at room temperature until all of the pyrazolidinone dissolved (usually within 45 min). The solvent was removed in vacuo, and the residue was taken up in 1,2-dichloroethane and concentrated again to give a colorless foam which was dried in vacuo at room temperature. NMR (90 MHz, $CDCl_3$): δ 6.1–5.3 (m, 1), 4.9–4.2 (m, 3), 4.0–3.6 (m, 1), 3.5–3.1 (m, 1), 1.4 (s, 9). IR (KBr): 3379, 1705, 1524, 1519, 1504, 1455, 1393, 1368, 1297, 1252, 1166 cm^{-1}. FDMS: M$^+$ 213 (strong), 426 (weak).

A solution of the above-prepared ylide precursor (20 mmol) in 1,2-dichloroethane or acetonitrile (80 mL) was treated with acetylene **9** (20 mmol) and heated to reflux for the time indicated. Progress of the reaction was monitored by TLC (3:2:1 toluene/chloroform/methanol) and was judged complete when the "ylide precursor" had been consumed. The mixture was cooled, any insoluble material was removed by filtration, and the filtrate was concentrated in vacuo. The cycloadducts **10** and **11** were isolated by flash chromatography or preparative HPLC.

Bicyclic Pyrazolidinone 10a. As above, pyrazolidinone **7** (24.8 mmol) was treated with formaldehyde (24.8 mmol) followed by refluxing with dimethyl butynedioate (**9a**) (3.52 g, 24.8 mmol) in 1,2-dichloroethane (100 mL) for 4 h. The crude reaction mixture was recrystallized from hexane–ethyl acetate to give 7.8 g (88%) of **10a** as a yellowish tinted powder. NMR (90 MHz, $CDCl_3$): δ 5.1 (br s, 1), 4.70 (m, 1), 4.36 (d, 1, J = 12), 4.06 (t, 1, J = 7.5), 3.96 (s, 3), 3.84 (d, 1, J = 12), 3.76 (s, 3), 2.88 (dd, 1, J = 7.5, 11), 1.48 (s, 9). IR ($CHCl_3$): 1759, 1709 cm^{-1}. FDMS: M$^+$ 355. UV (ethanol): λ_{max} 345 (ϵ 7958). Anal. Calcd for $C_{15}H_{21}N_3O_7$: C, 50.70; H, 5.96;, N, 11.83. Found: C, 50.44; H, 6.15;, N, 11.97.

Bicyclic Pyrazolidinone 10b. As above, pyrazolidinone **7** (20 mmol) was treated with formaldehyde (20 mmol) followed by refluxing in acetonitrile (50 mL) with diallyl butynedioate (**9b**) (3.88 g, 20 mmol) for 3 h. Preparative HPLC on silica gel (2:1 hexane/ethyl acetate) gave 2.67 g (33%) of the desired **10b**. NMR (90 MHz, $CDCl_3$): δ 6.20–5.70 (m, 2, unsaturated protons on allyl groups), 5.52–5.0 (m, 5, C-7 proton and unsaturated protons on allyl group), 4.82 (dm, 2, J = 6, saturated protons on allyl group on C-2 carboxylate), 4.64 (dm, 2, J = 6, saturated protons on allyl group on C-3 carboxylate group), 4.38 (d, 1, J = 13, C-4 proton), 4.04 (t, 1, J = 8, C-6 proton), 3.92 (d, 1, J = 13, C-4 proton), 2.88 (dd, 1, J = 8, 12, C-6 proton), 1.45 (s, 9, protons of t-Bu group); UV (methanol): λ_{max} 345 (ϵ 8500). IR ($CHCl_3$): 1750, 1736, 1709 cm^{-1}. Anal. Calcd for $C_{19}H_{25}O_7N_3$: C, 56.01; H, 6.19; N, 10.31. Found: C, 56.24; H, 6.35; N, 10.10.

---

(23) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28.

(24) Hall, R. G.; Trippett, S. *Tetrahedron Lett.* **1982**, *23*, 2603.

(25) Kishida, Y.; Nakamura, N. *Chem. Pharm. Bull.* **1969**, *17*, 2424. The allyl ester was prepared by substituting allyl alcohol for ethanol.

(26) Warrener, R. N.; Cain, E. N. *Aust. J. Chem.* **1971**, *24*, 785.

(27) Shen, M.; Schultz, A. G. *Tetrahedron Lett.* **1981**, *22*, 3347.

Bicyclic Pyrazolidinones 10c and 11c. As above, pyrazolidinone **7** (153 mmol) was treated with formaldehyde (153 mmol) followed by refluxing with allyl methyl acetylenedicarboxylate (**9c**) (23.46 g, 139 mmol) in 1,2-dichloroethane (150 mL) for 4 h. Flash chromatography (1:1 hexane/ethyl acetate) gave 3.69 g of the more polar isomer (**10c**) and 16.3 g of a mixture of the two regioisomers (38%). The mixture was subjected to preparative HPLC (ethyl acetate in hexane, 0 to 40% gradient) to give 3.4 g of pure less polar isomer **11c**. The less polar isomer **11c** was a yellow powder, mp 123–127 °C. NMR (90 MHz, $CDCl_3$): δ 6.10–5.60 (m, 1), 5.50–5.04 (m, 3), 4.70 (br m, 1), 4.56 (dm, 2, J = 5, C-1 (saturated) protons of allyl group), 4.40–3.56 (m, 3, the C-4 protons and one of C-6 protons), 3.84 (s, 3, methyl protons of methyl ester), 2.84 (dd, 1, J = 9, 12, one of C-6 protons), 1.36 (s, 9, methyl protons of *t*-Bu group). MS: M^+ 381. UV (methanol): λ_{max} 345 (ϵ 7950). IR ($CHCl_3$): 1753, 1709, 1438, 1377, 1371, 1280, 1234, 1215, 1163 cm^{-1}. Anal. Calcd for $C_{17}H_{23}O_7N_3$: C, 53.54; H, 6.08; N, 11.02. Found: C, 53.73; H, 6.08; N, 10.87.

The more polar isomer **10c** was recrystallized from benzene/hexane to give yellow needles, mp 119–124 °C. NMR (90 MHz, $CDCl_3$): 6.2–5.6 (m, 1), 5.50–5.04 (m, 3), 4.78 (dm, 2, J = 5, C-1 protons (saturated) of allyl group), 4.60 (br m, 1), 4.40–3.70 (m, 3, C-4 protons and one of C-6 protons), 3.66 (s, 3, protons of methyl group of methyl ester), 2.83 (dd, 1, J = 8, 12, one of C-6 protons), 1.36 (s, 9, methyl protons of *t*-BuO group). MS: M^+ 381. UV (methanol): λ_{max} 345 (ϵ 7300). IR ($CHCl_3$): 1750, 1737, 1710, 1417, 1370, 1285, 1234 cm^{-1}. Anal. Calcd for $C_{17}H_{23}O_7N_3$: C, 53.54; H, 6.08; N, 11.02. Found: C, 53.69; H, 6.05; N, 10.73.

Bicyclic Pyrazolidinones 10d and 11d. As above, pyrazolidinone **7** (58.3 mmol) was treated with formaldehyde (58.3 mmol) followed by refluxing with allyl 4-oxopentynoate (**9d**) (12.4 g, 58.3 mmol) in 1,2-dichloroethane for 4 h. Preparative HPLC on silica gel (ethyl acetate in hexane, 0 to 50% gradient) gave 5.51 g (26%) of the desired cycloadduct as a ca. 2:3 mixture of regioisomers **10d**:**11d**. A portion of this material was subjected to preparative TLC (1:1 hexane/ethyl acetate) to separate the regioisomers. Less polar isomer **11d**. NMR (90 MHz, $CDCl_3$): δ 6.08–5.64 (m, 1), 5.42–5.04 (m, 3), 4.92–4.5 (m, 1), 4.60 (d, 2, J = 6), 4.3 (d, 1, J = 12), 4.0 (t, 1, J = 7), 3.83 (d, 1, J = 12), 3.06–2.76 (dd, 1, J = 7, 12), 2.52 (s, 3), 1.43 (s, 9). The more polar isomer **10d** was recrystalized (hexane/ethyl acetate), mp 124–126 °C. NMR (90 MHz, $CDCl_3$): δ 6.22–5.76 (m, 1), 5.54–5.00 (m, 3), 4.84 (d, 2, J = 6), 4.92–4.50 (m, 1), 4.38 (d, 1, J = 12), 4.0 (t, 1, J = 7), 3.83 (d, 1, J = 12), 2.96–2.68 (dd, 1, J = 7, 12), 2.25 (s, 3), 1.43 (s, 9). FDMS: M^+ 365. UV (ethanol): λ_{max} 365 (ϵ 8478). IR ($CHCl_3$): 1716, 1657, 1376, 1370, 1344 cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.35; N, 11.50. Found: C, 55.70; H, 6.54;, N, 11.67.

Bicyclic Pyrazolidinones 10e and 11e. As above, pyrazolidinone **7** (20.8 mmol) was treated with formaldehyde (20.8 mmol) and then refluxed with allyl 4-oxo-4-phenylbutynoate (**9e**) (4.45 g, 20.8 mmol) in 1,2-dichloroethane (50 mL) for 6 h. Flash chromatography on silica gel (0–40% ethyl acetate in hexane gradient) gave 0.47 g of the less polar isomer **10e**, 0.51 g of a mixture of regioisomers, and 1.60 g of the more polar isomer **11e**, total yield of cycloadducts was 29%. Less polar isomer **10e**. NMR (90 MHz, $CDCl_3$): δ 7.76–7.28 (m, 5), 5.77–5.32 (m, 1), 5.26–5.00 (m, 2), 4.93–4.58 (m, 1), 4.56–3.95 (m, 5), 2.86 (dd, 1, J = 8, 11), 1.43 (s, 9). IR ($CHCl_3$): 1744, 1715, 1500, 1413, 1370, 1347 cm^{-1}. UV (methanol): λ_{max} 375 (ϵ 6774), 245 (9285). MS: $(M - 57)^+$ 370. Anal. Calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.90; N, 9.83. Found: C, 62.03; H, 6.20; N, 9.54. More polar isomer **11e**. NMR (90 MHz, $CDCl_3$): δ 8.00–7.79 (m, 2), 7.72–7.31 (m, 3), 5.80–5.35 (m, 1), 5.28–4.90 (m, 3), 4.94–4.31 (m, 4), 4.14–3.89 (m, 2), 2.98 (dd, 1, J = 8, 11), 1.40 (s, 9). IR ($CHCl_3$): 1707, 1502, 1370 cm^{-1}. UV (ethanol) λ_{max} 344 nm (ϵ 7173), 257 (12 783). FDMS: $(M + 1)^+$ 428, M^+ 427. Anal. Calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.90; N, 9.83. Found: C, 61.97; H, 5.84; N, 9.69.

Bicyclic Pyrazolidinones 10f and 11f. As above, pyrazolidinone **7** (10 mmol) was treated with formaldehyde (10 mmol) followed by refluxing with *tert*-butyl 3-(phenylcarbamoyl)propiolate (**9f**) (2.45 g, 10 mmol) in 1,2-dichloroethane (20 mL) for 6 h. Flash chromatography on silica gel (7:3 hexane/ethyl acetate) gave 600 mg of the less polar isomer **10f** and 550 mg of the more polar isomer **11f** both as yellow foams. Total yield of cycloadducts: 25%. Less polar isomer **10f**. NMR (90 MHz, $CDCl_3$): δ 7.6–6.92 (m, 5), 5.18 (br d, 1), 4.72 (m, 1), 4.64 (d, 1, J = 14), 4.04 (t, 1, J = 8), 3.84 (d, 1, J = 14), 2.76 (dd, 1, J = 8 and 12), 1.56 (s, 9), 1.42 (s, 9). IR ($CHCl_3$): 1711, 1704, 1658 cm^{-1}. UV (ethanol): λ_{max} 337 (ϵ_{max} 6490), 229 (11 120). FDMS: M^+ 458. More polar isomer **11f**: NMR (90 MHz, $CDCl_3$): δ 9.4 (br s, 1), 7.7–6.96 (m, 5), 5.36 (br d, 1, J = 6), 4.70 (m, 1), 4.31 (d, 1, J = 13), 3.97 (t, 1, J = 8), 3.82 (d, 1, J = 13), 2.90 (dd, 1, J = 8 and 12), 1.44 (s, 18). IR ($CHCl_3$): 1692 cm^{-1}. UV (ethanol): λ_{max} 337 (ϵ_{max} 8461), 239 (13 505). FDMS: M^+ 458.

Bicyclic Pyrazolidinone 10g. As above, pyrazolidinone **7** (8 mmol) was treated with formaldehyde (8 mmol) followed by refluxing with allyl 3-(dimethoxyphosphinyl)propynoate (**9g**) (1.74 g, 8 mmol) in 1,2-dichloroethane (50 mL) for 2.5 h. Preparative HPLC on silica gel (60–100% ethyl acetate in hexane gradient) gave 1.6 g (46%) of **10g** as a yellow gum. NMR (90 MHz, $CDCl_3$): δ 6.2–5.8 (m, 1), 5.6–5.0 (m, 3), 4.84 (dm, 2, J = 6), 4.7 (m, 1), 4.4 (dd, 1, J = 3, 12), 4.05 (m, 1), 3.85 (dd, 1, J = 3, 12), 3.84 (s, 3), 3.72 (s, 3), 2.90 (dd, 1, J = 9, 12), 1.5 (s, 9). MS: M^+ 431. UV (95% ethanol): λ_{max} 321 (ϵ 5090). IR ($CHCl_3$): 1714, 1502, 1055, 1038 cm^{-1}. Anal. Calcd for $C_{17}H_{25}O_8N_3P$: C, 47.33; H, 6.08; N, 9.74; P, 7.18. Found, C, 47.29; H, 6.08; N, 9.58; P, 6.90.

Bicyclic Pyrazolidinone 10h. *tert*-Butyl 4,4,4-trifluoro-3-oxo-2-(triphenylphosphoryl)butanoate[28] (14.16 g, 30 mmol) was slurried in 50 mL of silicone oil containing 2,6-di-*tert*-butyl-4-methylphenol (30 mg). Nitrogen was bubbled through the stirred slurry for 10 min, then with continued nitrogen flushing the mixture was heated to 260 °C, and the volatiles from this mixture were collected in a flask cooled to −78 °C, via a short-path still head. A crude distillate of approximately 1.55 g of yellow oil and some solid was collected. The distillate was immediately dissolved in 1,2-dichloroethane (15 mL) and added to the material derived from pyrazolidinone **7** (7 mmol) and formaldehyde (7 mmol). The resultant solution was refluxed for 21 h, cooled, filtered, and concentrated in vacuo. The concentrate was chromatographed on silica gel (30 g) eluted with 40% ethyl acetate in hexane to give 250 mg (9%) of **10h** as a yellow foam. NMR (90 MHz, $CDCl_3$): δ 5.36 (d, 1, J = 7), 4.7 (m, 1), 4.24 (dm, 1, J = 12), 3.96 (t, 1, J = 8), 3.8 (dm, 1, J = 12), 3.85 (m, 1), 1.45 (s, 9), 1.36 (s, 9). IR ($CHCl_3$): 1738, 1715, 1379, 1310 cm^{-1}. UV (95% ethanol): λ_{max} 310 (ϵ 4450). MS: $(M + 1)^+$ 408. Anal. Calcd for $C_{14}H_{24}O_5N_3F_3$: C, 50.12; H, 5.94; N, 10.31; F, 13.99. Found: C, 49.87; H, 5.88; N, 10.16; F, 13.84.

Bicyclic Pyrazolidinone 11i. As above, pyrazolidinone **7** (14.7 mmol) was treated with formaldehyde (14.7 mmol) followed by refluxing with allyl γ-[(tetrahydropyran-2-yl)oxy]tetrolate (**9i**) (3.3 g, 14.7 mmol) in 1,2-dichloroethane (45 mL) for 40 h. Flash chromatography on silica gel (0–40% ethyl acetate in hexane gradient) gave 0.66 g of **11i** and 0.28 g of the deprotected cycloadduct **11j**. Total yield of cycloadducts: 16%. Acid-catalyzed hydrolysis of **11i** gave only **11j**. **11i**. NMR (90 MHz, $CDCl_3$): δ 6.2–5.7 (m, 1), 5.5–4.4 (m, 7) with 4.68 (dm, 2, J = 6) superimposed; 4.4–3.4 (m, 5), 2.80 (dd, 1, J = 8, 11), 2.0–1.1 (m, 6) with 1.40 (s, 9) superimposed. IR ($CHCl_3$): 1713, 1369, 1261, 1250, 1215 cm^{-1}. FDMS: M^+ 437.

Bicyclic Pyrazolidinones 10j and 11j. As above, pyrazolidinone **7** (44.5 mmol) was treated with formaldehyde (44.5 mmol) followed by refluxing with allyl γ-hydroxytetrolate (**9j**) (6.23 g, 44.5 mmol) in 1,2-dichloroethane (50 mL) for 18 h. Flash chromatography on silica gel (100% hexane to 100% ethyl acetate gradient) gave 2.36 g of the less polar isomer **11j** and 2.11 g of the more polar isomer **10j**. Total yield of cycloadducts: 28%. Less polar isomer **11j**. NMR (90 MHz, $CDCl_3$): δ 6.12–5.67 (m, 1), 5.58–5.12 (m, 3), 4.82 (s, 1), 4.86–4.52 (m, 3), 4.24 (d, 1, J = 11), 3.97 (t, 1, J = 8), 3.76 (d, 1, J = 11), 2.92 (dd, 1, J = 8, 12), 1.40 (s, 9). IR (KBr): 3345 (br), 1711, 1691, 1535, 1434, 1367, 1286, 1268, 1239 cm^{-1}. UV (ethanol): λ_{max} 335 nm (ϵ 9553), 265 (886). FDMS: M^+ 353. More polar isomer **10j**. NMR (90 MHz, $CDCl_3$): δ 6.19–5.71 (m, 1), 5.51–5.10 (m, 3), 5.03–4.41 (m, 4), 4.47 (s, 1), 4.39–3.63 (m, 3), 2.75 (dd, 1, J = 9, 12), 1.43 (s, 9). IR (KBr): 3375 (br), 1715, 1522, 1392, 1368, 1276, 1250 cm^{-1}. UV (ethanol): λ_{max} 434 nm (ϵ 75), 283 (2078). FDMS: M^+ 353.

Bicyclic Pyrazolidinone 10k. As above, pyrazolidinone **7** (2 mmol) was treated with formaldehyde (2 mmol) followed by refluxing with allyl propiolate (**9k**) (220 mg, 2 mmol) in 1,2-di-

---

(28) Chemical Abstracts (*Chem. Abstr.* **1983**, *99*, 38008r) describes the synthesis of the *sec*-butyl ester of perfluorobutynoate.

chloroethane (10 mL) for 16 h. Preparative TLC on silica gel (3:2 ethyl acetate/hexane) gave after two elutions 150 mg (23%) of **10k** as a yellow gum. NMR (90 MHz, $CDCl_3$): δ 6.26 (t, 1 *J* = 2.5), 6.1–5.6 (m, 1), 5.5–5.1 (m, 3), 4.9 (br d, 2, *J* = 6), 4.58 (br t, 1), 4.18 (dd, 1, *J* = 2.5, 14), 4.05 (t, 1, *J* = 7), 3.64 (dd, 1, *J* = 2.5, 14), 2.86 (dd, 1, *J* = 7, 12), 1.4 (s, 9). IR ($CHCl_3$): 1710 cm^{-1}. UV (95% ethanol): λ_{max} 311 (ϵ 2150). MS: M^+ 323.

Bicyclic Pyrazolidinone 11l. As above, pyrazolidinone **7** (3.8 mmol) was treated with formaldehyde (3.8 mmol) followed by refluxing with allyl 3-phenylpropynoate (**9l**) (710 mg, 3.8 mmol) in acetonitrile (10 mL) for 8 h. Preparative TLC (silica gel, 1:1 hexane/ethyl acetate) gave 160 mg (10%) of **11l**. NMR (90 MHz, $CDCl_3$): δ 7.40 (m, 5), 5.96–4.94 (m, 3), 4.62 (m, 1), 4.50 (d, 2, *J* = 6), 4.40 (d, 1, *J* = 12), 4.04 (t, 1, *J* = 8), 3.92 (d, 1, *J* = 12), 2.81 (dd, 1, *J* = 8, 12), 1.40 (s, 9). MS: M^+ 399. UV (methanol): λ_{max} 350 (ϵ 6800), 245 (7600). IR ($CHCl_3$): 1708, 1369, 1362, 1277, 1230 cm^{-1}. Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.15; H, 6.31; N, 10.52. Found: C, 62.88; H, 6.40, N, 10.35.

Bicyclic Pyrazolidinone 11m. As above, pyrazolidinone 7 (10 mmol) was treated with formaldehyde (10 mmol) followed by refluxing with allyl 3-(phenylthio)propiolate (**9m**) (2.18 g, 10 mmol) in 1,2-dichloroethane (20 mL) for 18 h. Preparative HPLC on silica gel (0–40% ethyl acetate in hexane gradient) gave 1.04 (24%) of **11m** as a yellow powder. NMR (270 MHz, $CDCl_3$): δ 7.45 (m, 2), 7.30 (m, 3), 5.96 (m, 1), 5.32 (m, 2), 5.08 (br s, 1), 4.75 (d, 2, *J* = 6), 4.28 (d, 1, *J* = 12), 4.08 (t, 1, *J* = 8), 3.75 (d, 1, *J* = 12), 2.74 (dd, 1, *J* = 9, 12), 1.44 (s, 9). UV (methanol): λ_{max} 342 (ϵ 10 800). IR ($CHCl_3$): 1712, 1500, 1369, 1331 cm^{-1}. Anal. Calcd for $C_{21}H_{25}O_5N_3S$: C, 58.45; H, 5.84; N, 9.74; S, 7.43. Found: C, 58.70; H, 5.66; N, 9.45; S, 7.46.

Preparation of LY186826. Acylation of 10d. Under an argon atmosphere, ethyl acetate (18 mL) was cooled to 0 °C and dimethylformamide (0.74 mL, 9.6 mmol) was added. Phosphoryl chloride (0.62 mL, 6.6 mmol) was added and the solution was stirred at 0 °C for 1 h. [2-[[(Allyloxy)carbonyl]amino]thiazol-4-yl]-(2*Z*)-(methoxyimino)acetic acid (1.882 g, 6.66 mmol) was added to the solution and the solution was stirred for 2 h at 0 °C. In the meantime, a ca. 1:1 mixture of **10d** and **11d** (2.25 g, 6.16 mmol) was dissolved in trifluoroacetic acid (30 mL). The solution was stirred at room temperature for 5 min and then concentrated under reduced pressure. The concentrate was taken up in methylene chloride and reconcentrated in vacuo. The residue was dissolved in dry THF (70 mL), the solution was cooled to 0 °C, and bis(trimethylsilyl)trifluoroacetamide (6 mL) was added. This solution was stirred at 0 °C for 25 min and then the above prepared acid chloride **13** solution was added. After 40 min at 0 °C ethyl acetate (100 mL) was added and the solution was washed with 1 N hydrochloric acid (40 mL), saturated aqueous sodium bicarbonate solution (60 mL), and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The concentrate was absorbed onto silica gel and chromatographed with a gradient elution of 100% hexane to 100% ethyl acetate to give 0.73 g (22%) of acylated nucleus **14** and its corresponding regioisomer as a 1:1 mixture of isomers. Physical data for the mixture. NMR (90 MHz, $CDCl_3$): δ 8.35 (d, 1), 7.06 (s, 1), 6.20–5.60 (m, 2), 5.60–5.12 (m, 4), 4.82–4.50 (m, 4), 4.48–3.80 (m, 4), 3.89 (s, 3), 2.40–2.00 (m, 1), 2.50 and 2.25 (2 × s, 3). IR ($CHCl_3$): 1728, 1698, 1555, 1422, 1370, 1275, 1229, 1207, and 1045 cm^{-1}. UV (95% ethanol): λ_{max} 344 (ϵ 7102), 263 (14 575), 207 (22 602). FDMS: M^+ 533. Anal. Calcd for $C_{22}H_{24}N_6O_8S$: C, 49.62; H, 4.54; N, 15.78; S, 6.02. Found: C, 49.53; H, 4.74; N, 15.60; S, 6.00.

Deblocking of 14. Under an argon atmosphere, palladium(II) acetate (0.011 g, 0.049 mmol) was suspended in acetone (3 mL) and triphenylphosphine (0.044 g, 0.17 mmol) was rinsed into the mixture with additional acetone (1 mL). The mixture was stirred at room temperature for approximately 5 min, when a precipiate formed. A 1:1 mixture of **14** and the corresponding 2,3 regioisomer (0.300 g, 0.563 mmol) was added as an acetone solution (10 mL). The solution was stirred for 35 min and then cooled to 0 °C. Tri-*n*-butyltin hydride (0.30 mL, 1.12 mmol) was added and the solution was stirred at 0 °C for 15 min and then at room temperature for 25 min. The solution was cooled to 0 °C, 1 N hydrochloric acid (1.12 mL) was added, and the solution was stirred for an additional 5 min at 0 °C and for a few additional minutes without a cooling bath. The solution was filtered and water (50 mL) was added to the filtrate. The filtrate was washed with hexane (2×, 50 mL) and then filtered through Celite. The aqueous solution was washed with ether (2×, 50 mL) and hexane (2×, 50 mL) and filtered through Celite, and the filtrate was lyophilized. The lyophilization yielded 0.21 g of crude product. A portion of the crude product (approximately 130 mg) was dissolved in water and chromatographed by HPLC on a reverse-phase C-18 column (silica gel) eluted with a mixture of 2% acetic acid and 5% acetonitrile in water to give 27 mg of LY186826. NMR (90 MHz, D_2O): δ 7.08 (s, 1), 5.32 (dd, 1, *J* = 7, 11), 4.54–3.80 (m, 2) with 4.30 (d, 1, *J* = 11) superimposed, 3.92 (s, 3), 3.20 (dd, 1, *J* = 8, 11), 2.26 (s, 3). IR (KBr): 1716, 1634, 1534, 1382, 1327, 1285 cm^{-1}. UV (ethanol): λ_{max} 352 (ϵ 9165), 299 (6728), 230 (15 607). MS: $(M + 1)^+$ 409.

Acknowledgment. We thank Dr. Noel Jones, John Swartzendruber, and Jack Dieter for obtaining X-ray crystallographic data and the physical chemistry department for providing analytical and spectral data. We are grateful to Dave Preston, Dr. John Ott, Dr. Fred Counter, and Dr. Norris Allen for the biological evaluation of these compounds. Large quantities of pyrazolidinone **7** were prepared by Paul Pranc. We are especially indebted to Dr. Lowell Hatfield, Dr. Charles Barnett, and Professor Edward C. Taylor for helpful discussions.