Synthesis of 6-Vinylidenepenams

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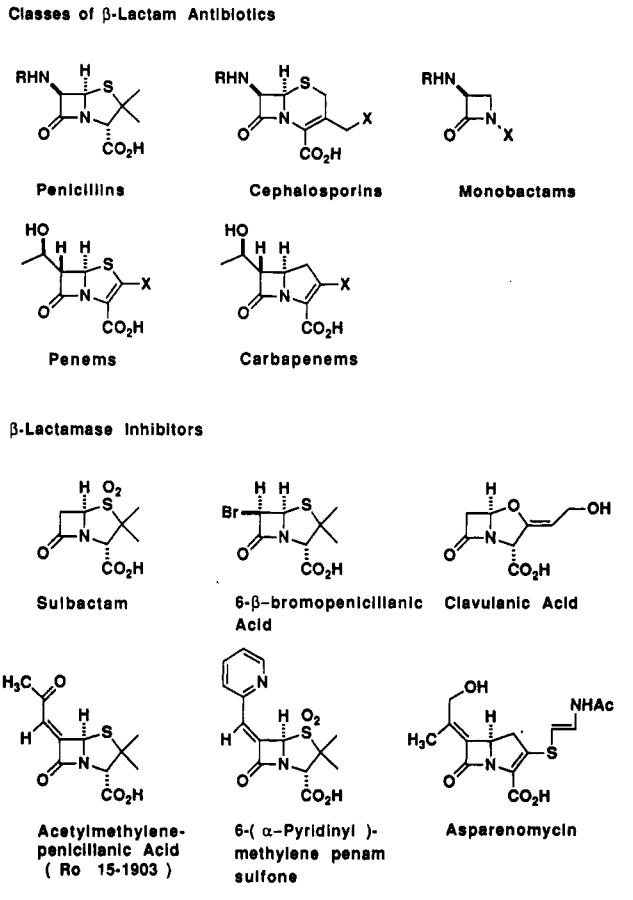
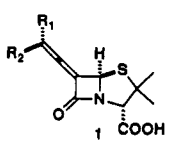
Received September 21, 1992

The preparation of unique penicillin derivatives containing an exocyclic allene at the 6 position (6-vinylidenepenams) is described. The synthetic scheme utilizes 6-oxopenicillinates as intermediates which stereospecifically add acetylide anions forming propargylic alcohols. Displacement of the corresponding propargylic triflates with higher order cuprate reagents and with copper(I) halides proceeds rapidly and stereospecifically. Halogen–metal exchange of the 6-(halovinylidene)penams is described. The derived allenyl anions can be trapped by electrophiles. Conversion of selected allyl and benzhydryl esters to the corresponding carboxylic acids is described. The β-lactamase inhibitory activity of the 6-(*tert*-butylvinylidene)penam sulfone is documented.

Penicillin-related antibiotics interfere with a critical series of proteases involved in bacterial cell wall construction.[1] There are many of these bacterial penicillin-binding proteins (PBP's), and the precise function of each of them is still not completely understood.[2] Penicillin resistance is often caused by the production of one of a series of enzymes collectively known as β-lactamases.[3] These secondary defensive enzymes cleave the reactive β-lactam portion of the antibiotic, rendering it ineffective at inhibiting the critical enzymes necessary for cell wall construction. Within the past decade, several pharmaceutical companies have developed drugs which act as β-lactamase inhibitors.[4] However, the inhibitors are individually active only against certain types of β-lactamase. For example, there are very few known inhibitors of class B, zinc-containing β-lactamases.[5] In many cases, the β-lactamase inhibitors have no direct antibiotic activity (i.e., they have no effect on the primary enzymes that are responsible for cell wall construction), but they serve to inactivate the defenses of the bacteria long enough for a second drug to locate its key enzymatic target. Examples of β-lactam antibiotics and β-lactamase inhibitors are shown below.[6] The known mechanisms of inhibition usually involve a nonreversible acylation of serine hydroxyl at an active site.[7]



We have developed several versatile synthetic routes that lead to the preparation of the previously unknown 6-vinylidenepenams **1**.[8] Allenes have been proven useful in the design of enzyme inhibitors and in the creation of drugs.[9] The 6-vinylidenepenams resemble known 6-*alkyl*-



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(6) It should be noted that, despite the existence and the threat of resistant strains, clinically the administration of the proper β-lactam antibiotic (without a β-lactamase inhibitor) is often sufficient.

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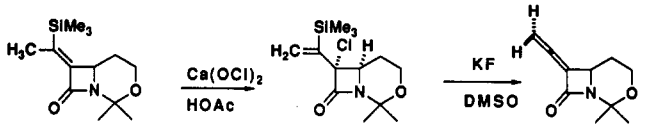
idene β-lactamase inhibitors (such as Ro 15-1903). In this paper, we will detail the preparation of the 6-vinylidenepenams and document the biological activity of one member of this class of β-lactamase inhibitors.

Results and Discussion

We have reported that α-vinylidene-β-lactam **2** is a stable, isolable species.[10] While exploring the chemistry of α-(silylmethylene) β-lactam **3**, we noticed that reaction with hypochlorous acid produced the chlorinated olefin **4** rather than the expected chlorohydrin.[11] This material, when treated with fluoride, produced the allene **2** in 60% yield. With this knowledge, we set out to devise a preparation of 6-vinylidenepenams using 6-oxopenicillinates (and their addition compounds) as key intermediates.



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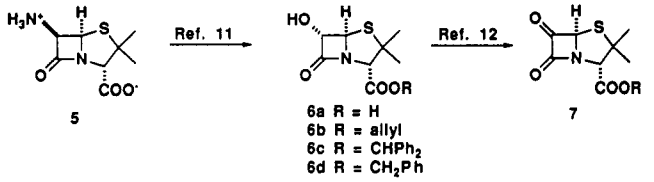
We synthesized 6-hydroxypenicillanic acid (6-HPA, **6a**) from 6-aminopenicillanic acid[12] (6-APA, **5**) as shown in Scheme I. It is obtained as an amorphous powder, which decomposed during all purification attempts. **6a** is not stable to heat and must be stored at −20 °C. Esterification typically produced only modest yields of the corresponding esters.

While oxidation of the 6-hydroxypenicillinates via the Swern method[13] is straightforward, the 6-oxo derivatives (**7**) that are produced are unstable at pH ≥ 7. Therefore, the reaction mixture should only be washed with saturated aqueous ammonium chloride or with other suitably buffered aqueous solutions. Unlike previous workers,[14] we were unable to purify these compounds by column chromatography, and the crude materials were used as prepared. In certain cases (the allyl ester in particular), these 6-oxo derivatives were unstable toward prolonged storage at −20 °C.

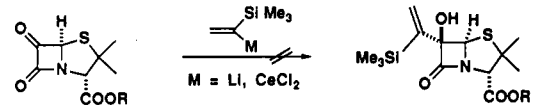
Our first approach to 6-vinylidenepenams envisioned the addition of an (α-metallovinyl)silane to ketone **7** followed by Chan elimination[15] to form the allene. However, the addition reaction failed to produce the expected product **8** as shown in Scheme II. When the reaction was performed carefully, that is at −100 °C in the case where M = Li, a single product could be isolated from the reaction mixture in moderate yield. This unstable material could

Scheme I



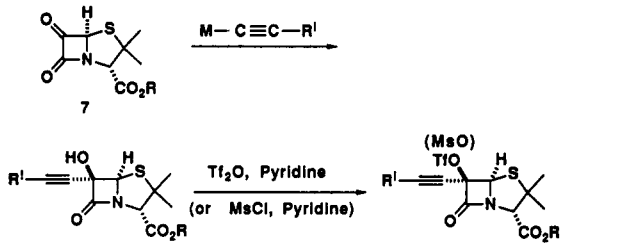
5 6a R = H 6b R = allyl 6c R = $CHPh_2$ 6d R = CH_2Ph 7

Scheme II



7 8

Scheme III



9	R^1 = H	10	R^1 = H
11	R^1 = Me	12	R^1 = Me
13	R^1 = *p*-SC_6H_4Cl	14	R^1 = *p*-SC_6H_4Cl
15	R^1 = $SiPh_3$	16	R^1 = $SiPh_3$
17	R^1 = CH_2OTBS	18	R^1 = CH_2OTBS
19	R^1 = $CH(OEt)_2$	20	R^1 = $CH(OEt)_2$
21	R^1 = CO_2Et	22	R^1 = CO_2Et
23	R^1 = CH(Ph)OTBS	24	R^1 = CH(Ph)OTBS
25	R^1 = $CH_2\underline{NCO(CH_2)_3}$	26	R^1 = $CH_2\underline{NCO(CH_2)_3}$

R = allyl, benzhydryl, or benzyl (see experimental)

be purified by column chromatography (with loss of material). This compound was shown spectroscopically to contain the trimethylsilyl group as well as a carbon-13 absorption at 227.7 ppm. Presumedly this signal was due to a hindered ketone. Several attempts to obtain crystals suitable for X-ray analysis were unsuccessful, and the process was not further pursued.

Our second attempt utilized propargyl alcohols prepared via metal acetylide addition to the ketones **7**, as shown in Scheme III. These addition reactions proceeded well when M = Li, Mg, or Ce. As expected, the order of reactivity was Li > Mg > Ce. Attempts to convert these alcohols to the desired allenes by intramolecular processes, e.g., by the 2,3-sigmatropic rearrangements of sulfenate esters, were unsuccessful. In most cases, however, the acetylenic alcohols could be converted to the corresponding triflates by treatment with triflic anhydride in the presence of pyridine.

Terminal acetylenes (R^1 = H) were the easiest to prepare. Substituted acetylenes could also be added to the 6-oxopenams at −78 °C, provided the ester was allyl or benzyl. The diphenylmethyl (benzhydryl) esters led to recovered ketone. We believe that the surprising reluctance of **7c** to undergo addition with substituted acetylenes is due to steric interference of the acetylenic substituent with the bulky diphenylmethyl group on the α face of the molecule. This result provides verification for our stereochemical assignment of the acetylenic alcohols. The acetylide adds exclusively from the convex, α, face. The problem of

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Scheme IV

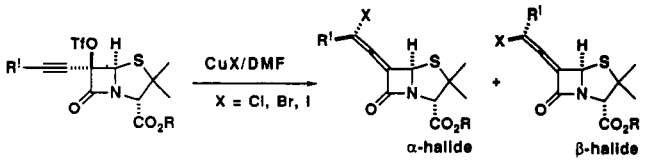

Table I. Data for the Reaction in Scheme IV. Yields Refer to Purified Materials

compd	R	R'	X	α:β	method	yield (%)
27b	allyl	H	I	100:0	CuX/DMF	38
27c	$CHPh_2$	H	I	100:0	CuX/DMF	47
27d	CH_2Ph	H	I	100:0	CuX/DMF	50
28b	allyl	H	Br	100:0	CuX/DMF	78
28c	$CHPh_2$	H	Br	100:0	CuX/DMF	30
28d	CH_2Ph	H	Br	100:0	CuX/DMF	41
29b	allyl	Me	I	100:0	CuX/DMF	42
30b	allyl	Me	Br	50:50	CuX/LiX/THF	95
31b	allyl	CH_2OTBS	I	50:50	CuX/LiX/THF	89
31c	$CHPh_2$	CH_2OTBS	I	50:50	CuX/LiX/THF	42
32b	allyl	$CH(OEt)_2$	I	50:50	CuX/LiX/THF	58
33b	allyl	CO_2Et	I	50:50	CuX/LiX/THF	40
34c	$CHPh_2$	CH(Ph)OTBS	I	50:50	CuX/DMF	68

production of benzhydryl ester derivatives was overcome by using the more reactive acetylide, M = Li, while allowing the reaction mixture to warm before quenching.

In an effort to obtain a crystalline allene suitable for X-ray analysis and to make the allene functionality more reactive, several substituted acetylenes were added to the 6-oxopenicillinates. The acetylenes having R' = Me, $SiPh_3$, CH_2OTBS, CH(Ph)OTBS, $CH(OEt)_2$, CO_2Et, and *p*-SC_6H_4Cl were prepared, and they were added to the ketone in the usual manner. Triflates which were stable to column chromatography could not be prepared from the [(*p*-chlorophenyl)thio]acetylide adduct, but a stable mesylate was prepared.

These propargylic triflates (and mesylate) were excellent substrates for conjugate addition by several copper(I) halides (CuX) and by higher order organocuprates. These additions lead to a variety of substituted 6-vinylidenepenams. Halo derivatives (Cl, Br, or I) could be prepared, but the chloro derivatives were unstable at room temperature and on silica gel. With terminal acetylenes (R' = H), a single isomer of the haloallene was easily prepared by treating the triflate with CuX in DMF at room temperature. With many substituted acetylenes, however, a mixture of diasteriomers resulted. The loss of selectivity is possibly due to racemization of the allenyl halide after its formation. When a single diasteriomer of the allenyl halide was treated with excess CuX/DMF for several hours, epimerization of the allenyl substituent did occur. The CuX/LiX system that was employed by Vermeer[16] led to mixtures of diasteriomers with both terminal and substituted acetylenes. The results are shown in Scheme IV and Table I.

With higher order cuprates, a single isomer was obtained as shown in Scheme V. This demonstrates the high specificity of the higher order cuprates for anti-displacement on these acetylenic substrates.[17] The reaction time

Scheme V

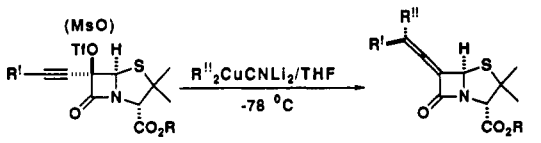

Table II. Data for the Reaction Shown in Scheme V. Yields Refer to Purified Materials

compd	R	R'	R''	yield (%)
35b	allyl	H	*tert*-butyl	47
35c	$CHPh_2$	H	*tert*-butyl	38
35d	CH_2Ph	H	*tert*-butyl	60
36b	allyl	H	Me	72
36c	$CHPh_2$	H	Me	30
36d	CH_2Ph	H	Me	60
37d	CH_2Ph	H	Ph	54
38b	allyl	H	*o*-MeOPh	49
39b	allyl	*p*-SC_6H_4Cl	*tert*-butyl	64
40d	CH_2Ph	$SiPh_3$	Me	50
41b	allyl	Me	Me	44
42b	allyl	Me	Ph	59
43b	allyl	Me	*tert*-butyl	80
44c	$CHPh_2$	$CH_2NCO(CH_2)_3$	Ph	78
45c	$CHPh_2$	$CH_2NCO(CH_2)_3$	*tert*-butyl	72

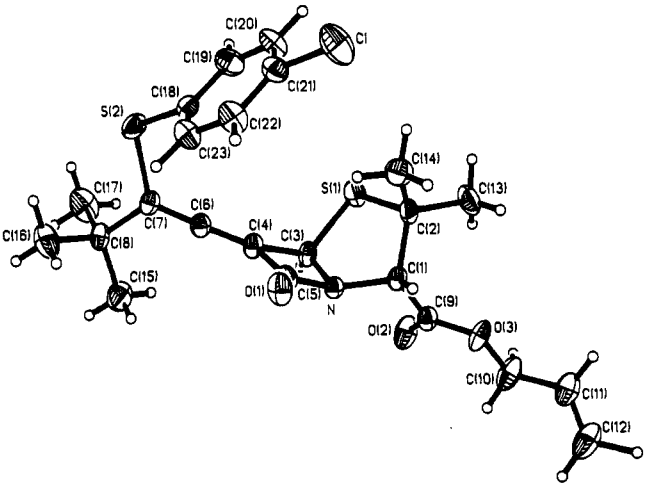

Figure 1. Crystal structure of **39b**.

proved to be a critical variable for this reaction (typically 1–5 min at −78 °C). Several types of normal cuprates were prepared, and all produced vinylidenes; see Table II. One exception resulted when methyl cuprate was added to triflate **26c**. In this case, there was a direct displacement of the triflate. In all cases, the reaction was shown to be highly stereospecific. We were able to obtain a crystal suitable for X-ray characterization from the product of the addition of the *tert*-butyl cuprate to the sulfur-substituted propargylic triflate. The structure is shown in Figure 1. In addition to the cuprates, several heteroatom (N, S, Se, Si, and Sn) anions (as Cu, K, Li, or Na salts) were prepared, and the anions were added to triflate **10**. There was no evidence of allene production with any of these reagents.

A strategy to prepare the terminally unsubstituted allene (i.e., R' = R'' = H) was developed. Several methods of introducing hydride directly (including sources of CuH) were explored, and several transition metal mediated methods for removing the halogen of the haloallenes were tried. Both routes were unsuccessful. However, direct halogen–metal exchange proved to be a more productive avenue.

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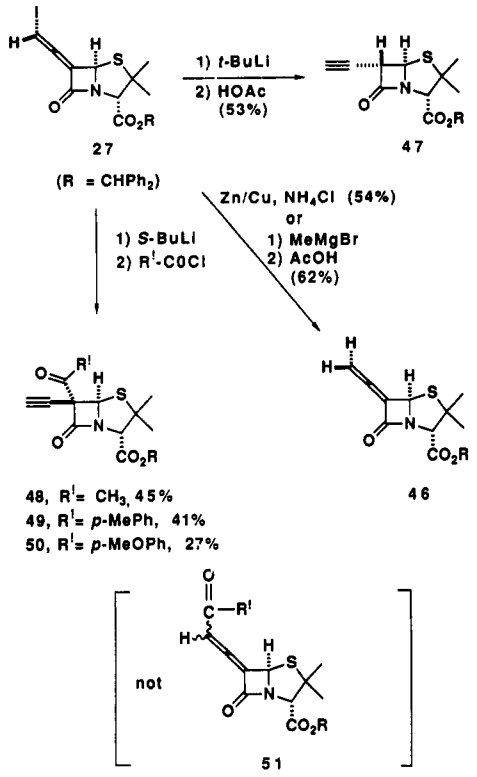
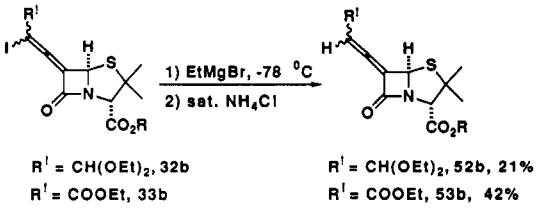
Scheme VI



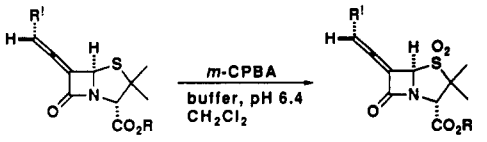
Scheme VII



The treatment of the iodoallene, **27c**, with Zn–Cu couple in methanolic NH_4Cl led to the parent unsubstituted vinylidene penam **46c** in 54% yield, Scheme VI. This material could also be prepared by the reaction of **27c** with CH_3MgBr after quenching of the intermediate allenylmagnesium bromide with acetic acid. The lithiation of **27c** with *tert*-butyllithium and quenching after 10 min produced the isomeric acetylene **47c**. Reaction with other electrophiles, including acyl halides, was also explored. Acylation of the intermediate organolithium led to production of the 6-acyl-6-acetylenic penams **48c–50c** (R' = Me, *p*-MeC_6H_4, *p*-$MeOC_6H_4$). Acylation of the allenylmagnesium intermediate was much slower but also produced the acetylenic compound **48c** in low yield. The terminally acylated derivative **51c** could not be formed by using this reaction sequence.

As shown in Scheme VII, terminally acylated vinylidenepenams could be prepared by incorporating the (protected) carbonyl into the acetylene. These acetylenic anions were added to the 6-oxopenicillinate, the resulting alcohol converted to the triflate, and the triflate displaced in the conjugate sense with CuI. When the electron-withdrawing group was attached to the allene, the Zn–Cu couple could not be used to reduce the iodoallene. In these instances, the procedure of choice was halogen–metal exchange with an organomagnesium reagent, Scheme VII. The yields in this sequence were modest. These very sensitive materials were prepared as a mixture of diastereomers.

Scheme VIII



Scheme IX

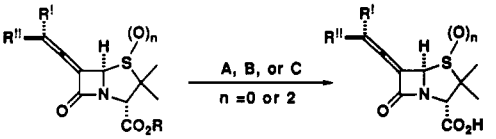


Table III. Data for the Reaction Shown in Scheme VIII. Yields Refer to Purified Materials

	R	R'	yield (%)
54c	$CHPh_2$	H	90
55b	allyl	Me	32
55d	CH_2Ph	Me	62
56b	allyl	*tert*-butyl	70
56d	CH_2Ph	*tert*-butyl	62
57b	allyl	*o*-MeOPh	22

In an attempt to make more highly functionalized 6-vinylidenepenams, compounds **31b,c**, **32b**, and **34c** were prepared. Several attempts to convert **31b,c** and **34c** to the corresponding alcohol and compound **32b** to its corresponding aldehyde as the substituent on allene were unsuccessful.

As a number of penam sulfones have been reported as potent β-lactamase inhibitors, the *m*-CPBA oxidation of these studies was performed as shown in Scheme VIII. Results are summarized in Table III. This reaction failed to produce sulfones of halovinylidenes (see Table I) and alkylvinylidenes such as **37d**, **39b**, and **41b–44c**. Other oxidizing agents such as $KMnO_4$ in AcOH–H_2O, oxone, and *tert*-butyloxone were also unsuccessful.

The final step involves deprotection of the ester to produce the free carboxylic acid or the corresponding carboxylate salt. The attempts to deprotect the benzyl group by usual methods were uniformly unsuccessful. The allyl esters were readily removed by $Pd(PPh_3)_4$, PPh_3, and acetic acid at rt to prepare compounds **35a**, **56a**, **39a**, and **42a**. This procedure failed to deprotect unsubstituted vinylidene, halovinylidenes (**27b** to **33b**), vinylidene having electron-withdrawing group **53b**, and vinylidene sulfones such as **55b** and **57b**. Attempts to remove the allyl group using other Pd reagents were unsuccessful.

The benzhydryl group was readily removed by stirring the ester for a short time either with anisole–TFA at 0 °C or with anisole–$AlCl_3$ at −78 °C. The latter method produced carboxylate salts in higher yields. The compounds **46a**, **28a**, and **44a** shown in Table IV were prepared by this procedure. However, this method also failed to deprotect iodovinylidenes and alkylvinylidenes such as **35c** and **36c**.

Biological Activity

A detailed study of the biological activity of this class of materials is in progress. Surprisingly, one of the most active of these compounds was 6-[(α)-*tert*-butylvinylidene]-penicillinic acid sulfone, **56a**. In a preliminary survey of biological activity, **56a** was able to inhibit the β-lactamase

Table IV. Data for the Deprotection of the Carboxylic Acids

	R'	R''	n	method[a]	yield (%)
46a	H	H	0	A	50
28a	Br	H	0	C	39
35a	*t*-Bu	H	0	B	21
56a	*t*-Bu	H	2	B	36
39a	*t*-Bu	*p*-ClPhS	0	B	85
42a	Ph	CH_3	0	B	38
44a	Ph	$CH_2\underline{NCO}(CH_2)_3$	0	A	55

[a] Method A: R = $CHPh_2$), $AlCl_3$, anisole, −78 °C; method B: R = allyl, $Pd(PPh_3)_4$, PPh_3, AcOH, rt; method C: R = $CHPh_2$, TFA, anisole, 0 °C.

derived from *Enterobacter cloacae* P99.[18] When a solution of 1.0 μg/mL of this enzyme was treated with 1 μg/mL of **56a**, 56% inhibition was observed [using a solution of cephalothin (1 mL of a 2.46 mM solution) as substrate and observing the band at 292 nm]. 100% inhibition could be obtained when the corresponding solution was treated with 10 μg/mL of the inhibitor. As a control, tazobactam, a highly potent β-lactamase inhibitor, was found to exhibit 56% inhibition at a concentration of 2 μg/mL. Further details of this assay can be found in the Experimental Section.

Conclusion

In conclusion, we have demonstrated the preparation of a number of 6-vinylidenepenams. We have also reported methodology for preparing several derivatives. Halogen–metal exchange of the 6-(halovinylidene)penam has been achieved. Some of these chiral allenes show activity as inhibitors of the β-lactamase derived from *E. cloacae* P99.

Experimental Section

Melting points were uncorrected and determined on a Mel-Temp capillary melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP200SY spectrometer. Proton chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (0.0). Carbon chemical shifts are reported in parts per million (δ) by using *d*-chloroform (77.0) as the reference. In the cases where inseparable diastereomers are present, spectral data for the mixture are reported with signals for the same carbon of each diasteriomer grouped together when they are recognizable.

Mass spectral data were obtained by either EI or FAB techniques. TLC was performed on Merck 0.2-mm Kieselgel 60 F_{254} silica-coated plastic plates. The compounds were identified in one or more of the following manners: UV (254 nm), I_2 chamber, and/or phosphomolybdic acid spray reagent. Flash chromatography was performed by using thick-walled glass columns and Merck 0.040–0.063-mm Kieselgel 60 silica gel. The glassware that was used in the reactions described below was oven or flame dried, and then it was cooled under Ar.

The chromatography solvents were distilled from CaH_2 before use. All additional solvents were obtained from Aldrich in Sure-Seal bottles. All reagents were used as received from Aldrich unless otherwise noted. The yields were generally reported after chromatography.

6α-Hydroxypenicillanic Acid (6a). 6α-Hydroxypenicillanic acid was prepared according to the procedure of Hauser and Sigg.[10] To a solution of 6-aminopenicillanic acid (216 g, 1.0 mol) in aqueous perchloric acid (215 mL of 70% acid in 1.5 L water) was added a cold solution of sodium nitrite (103.5 g, 1.5 mol) in water (1 L) over a period of 1 h while the temperature of the reaction mixture was maintained between 0 and −5 °C (ice–salt). The reaction was then stirred at this temperature for 20 min, and the product was extracted with ether (2 × 2.5 L). The combined ether layers were washed with water (1 × 500 mL) followed by saturated NaCl (1 × 100 mL), dried (Na_2SO_4), and concentrated (T < 35 °C) to yield **6a** (70 g, 32% yield) as a pale green fluffy solid: IR (Nujol mull) 3400–3300, 1732, 1623 cm^{-1}; ^1H NMR (1% CD_3OD in $CDCl_3$) δ 5.19 (1 H, s), 4.72 (1 H, s), 4.40 (1 H, s), 1.55 (3 H, s), 1.50 (3 H, s). This material was judged to be from 90 to 95% pure by ^1H NMR and was suitable for use in the following esterifications. This material slowly degenerated when stored at rt and rapidly decomposed if heated excessively during concentration. It appeared to be stable indefinitely at −20 °C.

Allyl 6α-Hydroxypenicillinate (6b). To a solution of 6α-hydroxypenicillanic acid (**6a**) (195.3 g, 0.9 mol) in dry DMF (1.8 L) at 0 °C was added triethylamine (315 mL, 2.25 mol). The solution was stirred for 15 min at this temperature, treated with allyl bromide (195 mL, 2.25 mol), and allowed to warm slowly to rt. After being stirred at rt overnight, the reaction mixture was washed with hexane (1.5 L) to remove excess allyl bromide, diluted with water (2 L), and extracted with ether (2 × 1 L). The combined ether layers were dried (Na_2SO_4), concentrated, and purified by column chromatography (1:9 EtOAc–CH_2Cl_2) to yield the desired **6b** (78 g, 34% yield) as a slightly yellow oil: R_f = 0.23 in 1:9 EtOAc/CH_2Cl_2; IR ($CDCl_3$) 3410, 1760, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05–5.86 (1 H, m), 5.50–5.30 (2 H, m), 5.30 (1 H, br s), 4.85 (1 H, br s), 4.75–4.65 (2 H, m), 4.50 (1 H, s), 1.61 (3 H, s), 1.46 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 171.7 (s), 167.4 (s), 131.0 (d), 119.6 (t), 84.9 (s), 71.1 (d), 68.7 (d), 66.2 (t), 63.8 (s), 33.3 (q), 25.7 (q).

Alternative Procedure for the Preparation of Allyl 6α-Hydroxypenicillinate (6b). To a 1-L flask with a stir bar under Ar was added 6-APA (100 g, 463 mmol), dry CH_2Cl_2 (500 mL), and distilled Et_3N (129 mL, 926 mmol). The mixture was stirred 2.5 h to dissolve the solid. Ethyl (or methyl) acetoacetate (59 mL, 463 mmol) was added dropwise via cannula. The mixture was stirred for 3 h and concentrated in vacuo. The clear slightly yellow viscous oil was dissolved in DMF (250 mL), and allyl bromide (44 mL, 509 mmol) was added in one portion. The mixture was stirred 13 h (Et_3NHBr precipitates) at rt. The reaction mixture was quenched with H_2O (400 mL) and 5:1 ether/CH_2Cl_2 (400 mL). The aqueous layer was extracted with additional 5:1 solution (3×, 100 mL). The combined organic layers were washed with water (2×, 125 mL) and saturated NaCl (2×, 125 mL). The slightly yellow solution was dried (Na_2SO_4) and concentrated in vacuo. The viscous oil was dissolved in dry acetone (200 mL), and a *p*-toluenesulfonic acid monohydrate (77.5 g, 407 mmol) in dry acetone (100 mL) solution was added in one portion. The mixture was shaken vigorously for 5 min and stirred rapidly as a solid formed. Dry ether (2.5 L) was added, and stirring was continued for 15 min. The solid was filtered and dried to give allyl 6-aminopenicillinate *p*-toluenesulfonate as a slightly yellow powder (133.72 g, 77% yield). To a three-necked flask (3 L) equipped with a mechanical stirrer and a dropping funnel was added water (1 L) and 70% perchloric acid (80 mL, 347 mmol). The mixture was cooled to 1 °C (ice–salt), and the powder (98.9 g, 231 mmol) from above was added in small portions over 10 min. A cooled solution of sodium nitrite (24 g, 347 mmol) in water (300 mL) was placed in the dropping funnel, and it was added dropwise over 30–45 min. The solution was stirred for 10 min after gas evolution had ceased (ca. 45 min). Ether (1 L) was added, and the solution was stirred rapidly for 10 min. The layers were separated, and the aqueous layer was extracted with ether (1 L). The combined organic layers were washed with saturated NH_4Cl (50 mL), saturated $NaHCO_3$ (50 mL), and pH = 7 buffer solution (2×, 50 mL). The solution was dried (Na_2SO_4), concentrated in vacuo, and chromatographed. There was obtained a very pure yellow-red viscous oil (19.64g, 33% yield) whose spectral properties were identical with those reported above. The reaction has been run on a scale that was triple the one given here with similar results.

Benzhydryl 6α-Hydroxypenicillinate (6c). **6a** (54.3 g, 0.25 mol) in ethyl acetate (500 mL) was cooled with ice, and diphenyldiazomethane[19] (48.5 g, 0.25 mol) in ether (250 mL) was

(18) This purified enzyme was purchased from the Centre for Applied Microbiology and Research (Porton Down, Wilts., U.K.) and used without further purification.

(19) Smith, L. E.; Howard, K. L. In *Organic Syntheses*; Drake, N. L., Ed.; Wiley: New York, 1944; Vol. 24, p 53.

added dropwise with stirring. After the addition was over, the mixture was stirred at rt for 5 h, concentrated, and purified by column chromatography (10% EtOAc in CH_2Cl_2) to afford the desired ester **6c** as a gum (40 g, 42% yield): R_f = 0.43 in 1:9 EtOAc/CH_2Cl_2; IR ($CHCl_3$) 3400, 1775, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (10 H, bs), 6.94 (1 H, s), 5.30 (1 H, s), 4.82 (1 H, bs), 4.57 (1 H, s), 4.00 (1 H, bs), 1.54 (3 H, s), 1.25 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 171.7 (s), 166.6 (s), 138.9 (s), 128.3, 128.1, 127.9, 127.3, 126.8, 84.7 (d), 78.4 (d), 71.1 (d), 68.7 (d), 63.9 (s), 33.2 (q), 25.1 (q).

Benzyl 6α-Hydroxypenicillinate (6d). This compound was prepared as described for **6b** using benzyl bromide. A colorless gum was obtained in 40% yield: R_f = 0.27 in 15% EtOAc in CH_2Cl_2; IR ($CHCl_3$) 3425, 1770, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (5 H, bs), 5.32 (1 H, bs), 5.20 (2 H, s), 4.85 (1 H, bs), 4.51 (1 H, s), 3.89 (1 H, bs), 1.54 (3 H, s), 1.39 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 171.0, 167.6, 135.0, 128.7, 85.1, 71.1, 68.8, 67.6, 33.3, 25.7.

Allyl 6-Oxopenicillinate (7b). TFAA (8.4 mL, 60 mmol) was added dropwise with stirring to a solution of DMSO (5.6 mL, 80 mmol) in anhydrous CH_2Cl_2 (80 mL) at −78 °C. After 20 min, a solution of **6b** (10.3 g, 40 mmol) in anhydrous CH_2Cl_2 (80 mL) was added to this slurry over 5 min, and the resultant mixture was stirred at −78 °C for 1 h. Triethylamine (16.6 mL, 120 mmol) was added dropwise, and the solution was stirred for 10 min. The cold reaction mixture was poured into a well-stirred, cold (0 °C) mixture of saturated aqueous ammonium chloride (NH_4Cl, 800 mL) and CH_2Cl_2 (80 mL). The layers were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (80 mL). The combined organic layers were washed once with saturated NH_4Cl, dried (Na_2SO_4), and concentrated to produce **7b** (10 g, 98% yield) as a pale yellow gum which was used without further purification: IR ($CHCl_3$) 1820, 1780, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.10–5.80 (1 H, m), 5.83 (1 H, s), 5.35–5.45 (2 H, m), 4.83 (1 H, s), 4.77–4.67 (2 H, m), 1.58 (6 H, bs); ^{13}C NMR ($CDCl_3$) δ 190.4 (s), 168.0 (s), 166.5 (s), 130.8 (d), 120.0 (t), 76.8 (d), 71.6 (d), 66.5 (t), 64.2 (s), 34.0 (q), 25.2 (q).

Benzhydryl 6-Oxopenicillinate (7c). This compound was prepared as described for **7b** (yield = 97%): IR ($CHCl_3$) 1820, 1775, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (10 H, bs), 7.00 (1 H, s), 5.83 (1 H, s), 4.91 (1 H, s), 1.56 (3 H, s), 1.36 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 190.4 (s), 168.0 (s), 165.8 (s), 139.1 (s), 138.6 (s), 128.5, 128.2, 127.6, 127.4, 127.1, 126.8, 126.5, 78.8 (d), 76.8 (d), 71.5 (d), 64.2 (s), 34.1 (q), 24.7 (q).

Benzyl 6-Oxopenicillinate (7d). This compound was prepared as described for **7b** (yield = 98%): IR ($CHCl_3$) 1825, 1780, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (5 H, bs), 5.81 (1 H, s), 5.26 (2 H, s), 4.84 (1 H, s), 1.55 (3 H, s), 1.49 (3 H, s).

Allyl 6α-Ethynyl-6β-hydroxypenicillinate (9b). Dry acetylene was bubbled into anhydrous THF (100 mL) at −78 °C under argon while a hexane solution of *n*-BuLi (2.5 M, 12 mL, 30 mmol) was added dropwise. After the addition was complete, acetylene was bubbled through the solution for an additional 10 min. A suspension[20] (stirred ≥3 h) of anhydrous $CeCl_3$ (8.7 g, 35 mmol) in anhydrous THF (150 mL) was cooled and added in one portion. The mixture was stirred at −78 °C for an additional 1 h. A cold (0 °C) solution of **7b** (6.12 g, 24 mmol) in dry THF (100 mL) was added dropwise by cannula, and the reaction was allowed to stir for an additional 1 h at −78 °C. It was then quenched with cold dilute AcOH, and the product was extracted with ether (2 × 100 mL). The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated. Column chromatography (CH_2Cl_2) afforded **9b** (2.13 g, 32% yield) as a yellow oil: R_f = 0.30 in CH_2Cl_2; IR ($CHCl_3$) 3410, 3300, 2105, 1780, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.00–5.75 (1 H, m), 5.64 (1 H, s), 5.25–5.50 (2 H, m), 4.60–4.75 (2 H, m), 4.55 (1 H, s), 2.84 (1 H, s), 1.61 (3 H, s), 1.53 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 168.2 (s), 167.1 (s), 130.9 (d), 119.8 (t), 83.5 (s), 80.8 (d), 76.8 (s), 75.5 (d), 68.8 (d), 66.3 (t), 63.6 (s), 33.4 (q), 25.5 (q).

Benzhydryl 6α-Ethynyl-6β-hydroxypenicillinate (9c). This compound was prepared as described for **9b** (yield = 45%): R_f = 0.30 in 5% EtOAc in CH_2Cl_2; IR ($CHCl_3$) 3430, 3300, 1778, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (5 H, bs), 7.36 (5 H, bs), 6.96 (1 H, s), 5.58 (1 H, s), 4.64 (1 H, s), 2.83 (1 H, s), 1.59 (3 H, s), 1.32 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 169.7 (s), 166.0 (s), 143.6 (s), 138.7 (s), 128.2, 128.0, 127.8, 127.1, 126.6, 126.2, 78.1, 77.5, 77.3, 76.0, 69.1 (d), 67.4 (s), 63.8 (s), 32.8 (q), 25.2 (q).

Benzyl 6α-Ethynyl-6β-hydroxypenicillinate (9d). This compound was prepared as described for **9b** (yield = 62%): R_f = 0.57 in CH_2Cl_2; IR ($CHCl_3$) 3410, 3310, 2120, 1785, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (5 H, bs), 5.66 (1 H, s), 5.29, 5.23, 5.22, 5.16 (2 H, ABq), 4.57 (1 H, s), 3.45 (1 H, bs), 2.83 (1 H, s), 1.59 (3 H, s), 1.45 (3 H, s).

Allyl 6α-Ethynyl-6β-(trifluoromethanesulfonato)penicillinate (10b). Trifluoromethanesulfonic anhydride (1.68 mL, 10 mmol) was added dropwise (3-s intervals) to a cold (0 °C) solution of pyridine (0.8 mL, 10 mmol) and **9b** (2 g, 7.12 mmol) in anhydrous $CHCl_3$ or CH_2Cl_2 (30 mL). The reaction mixture was allowed to warm to rt and monitored by TLC (reaction time = 0.5–12 h). After concentration, the dark residue was purified by column chromatography (CH_2Cl_2) to yield **10b** as a yellow oil (1.8 g, 61% yield): R_f = 0.75 in CH_2Cl_2; IR ($CHCl_3$) 3300, 2120, 1800, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05–5.85 (1 H, m), 5.71 (1 H, s), 5.41–5.25 (2 H, m), 4.67–4.62 (2 H, m), 4.61 (1 H, s), 3.30 (1 H, s), 1.58 (3 H, s), 1.48 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.0 (s), 161.0 (s), 130.8 (d), 119.7 (t), 117.8 (q, J = 320.85), 87.6 (s), 84.1 (d), 75.3 (d), 72.3 (s), 70.3 (d), 66.3 (t), 64.3 (s), 33.1 (q), 24.9 (q).

Benzhydryl 6α-Ethynyl-6β-(trifluoromethanesulfonato)penicillinate (10c). This compound was prepared as described for **10b** (yield = 44%): R_f = 0.63 in CH_2Cl_2; IR ($CHCl_3$) 3300, 2100, 1795, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (10 H, m), 6.96 (1 H, s), 5.77 (1 H, s), 4.72 (1 H, s), 3.23 (1 H, s), 1.62 (3 H, s), 1.31 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 165.5 (s), 161.1 (s), 138.7 (s), 128.6, 128.4, 128.3, 127.4, 127.1, 126.9, 117.8 (q, CF_3, J = 321.0), 87.6 (s), 84.0 (d), 78.8 (d), 75.5 (d), 72.3 (s), 70.4 (d), 64.6 (s), 33.3 (q), 24.8 (q).

Benzyl 6α-Ethynyl-6β-(trifluoromethanesulfonato)penicillinate (10d). This compound was prepared as described for **10b** (yield = 73%): R_f = 0.88 in CH_2Cl_2; IR ($CHCl_3$) 3300, 2125, 1800, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (5 H, bs), 5.75 (1 H, s), 5.32, 5.24, 5.22, 5.14 (2 H, ABq), 4.62, (1 H, s), 3.24 (1 H, s), 1.61 (3 H, s), 1.43 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.3, 161.1, 134.4, 128.8, 117.8 (CF_3, q, J = 320.3), 89.7, 87.6, 83.9, 75.4, 70.4, 67.7, 64.5, 33.3, 25.0.

Allyl 6α-propynyl-6β-hydroxypenicillinate (11b). This compound was prepared as described for **9b** (yield = 27%): R_f = 0.15 in CH_2Cl_2; IR ($CHCl_3$) 3420, 1780, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.00–5.80 (1 H, m), 5.60 (1 H, s), 5.50–5.29 (2 H, m), 4.80–4.59 (2 H, m), 4.54 (1 H, s), 3.43 (1 H, bs), 1.94 (3 H, s), 1.60 (3 H, s), 1.52 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 170.7, 166.8, 130.8, 119.5, 86.3, 78.1, 76.3, 73.4, 69.3, 66.0, 64.1, 33.3, 25.8, 3.7.

Allyl 6α-Propynyl-6β-(trifluoromethanesulfonato)penicillinate (12b). This compound was prepared from the alcohol **11b** as described for **10b** above (yield = 94%): R_f = 0.76 in CH_2Cl_2; IR ($CHCl_3$) 1798, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.00–5.80 (1 H, m), 5.66 (1 H, s), 5.45–5.23 (2 H,, m), 4.71–4.61 (2 H, m), 4.60 (1 H, s), 1.99 (3 H, s), 1.58 (3 H, s), 1.48 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.1 (s), 162.0 (s), 130.6 (d), 119.7 (t), 117.7 (CF_3, q, J = 320.5), 93.7 (s), 88.5 (s), 75.5 (d), 70.1 (d), 68.4 (s), 66.1 (t), 64.0 (s), 33.0 (q), 24.9 (q), 3.7 (q).

Allyl 6α-[[(*p*-Chlorophenyl)sulfenyl]ethynyl]-6β-hydroxypenicillinate (13b). This compound was prepared as described for **9b** by using [(*p*-chlorophenyl)sulfenyl]acetylene[21] (yield = 29%): R_f = 0.33 in CH_2Cl_2; IR ($CHCl_3$) 3400, 2150, 1780, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (4 H, s), 6.01–5.74 (1 H, m), 5.67 (1 H, s), 5.48–5.28 (2 H, m), 4.79–4.60 (2 H, m), 4.56 (1 H, s), 3.76 (1 H, bs), 1.62 (3 H, s), 1.53 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 169.6, 166.7, 132.8, 130.8, 129.3, 127.8, 119.5, 92.6, 76.8, 76.3, 69.3, 66.0, 64.0, 33.0, 25.6.

Allyl 6α-[[(*p*-Chlorophenyl)sulfenyl]ethynyl]-6β-(methanesulfonato)penicillinate (14b). Methanesulfonyl chloride (0.98 mL, 1.45 g, 10 mmol) was added dropwise to a chilled (0 °C) solution of acetylenic alcohol **13b** (4.24 g, 10 mmol) in dry pyridine (15 mL). The cooling bath was removed, and the reaction was stirred at ambient temperature for 4 h. It was diluted with water and extracted with CH_2Cl_2. The organic layer was washed

(20) All suspensions were prepared by allowing the anhydrous $CeCl_3$ to stir in THF for at least 3 h and preferrably overnight.

(21) Kleijn, H.; Vermeer, P. *J. Org. Chem.* **1985**, *50*, 5143 (see General Procedures section).

with 2 N HCl, 5% $NaHCO_3$, and water. After drying (Na_2SO_4) and concentration, the resulting oil was purified by column chromatography (CH_2Cl_2) to afford the mesylate **14b** as an oil (3.16 g, 63% yield): R_f = 0.62 in CH_2Cl_2; IR ($CHCl_3$) 2170, 1790, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (4 H, s), 6.02–5.81 (1 H, m), 5.75 (1 H, s), 5.47–5.21 (2 H, m), 4.71–4.64 (2 H, m), 4.60 (1 H, s), 3.25 (3 H, s), 1.64 (3 H, s), 1.49 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.4 (s), 163.0 (s), 133.6 (s), 130.8 (d), 129.7 (d), 128.6 (s), 128.1 (d), 119.9 (t), 88.9 (s), 84.2 (s), 82.9 (s), 76.0 (d), 70.3 (d), 66.3 (t), 63.8 (s), 41.3 (q), 33.0 (q), 25.5 (q).

Benzyl 6α-[(Triphenylsilyl)ethynyl]-6β-hydroxypenicillinate (15d). Ethylmagnesium bromide (2.0 M in Et_2O, 2.6 mL, 5.2 mmol) was added dropwise to a cold (−78 °C) solution of (triphenylsilyl)acetylene (1.48 g, 4.85 mmol) in dry THF (25 mL). The solution was stirred for an additional 5 min at −78 °C, and then it was warmed to rt over 30 min and cooled again to −40 °C. This cold solution was then added via cannula to a cold solution of **7d** (1.52 g, 5 mmol) in THF (15 mL) at −78 °C. It was warmed to −40 °C over 30 min and then quenched with cold saturated NH_4Cl. The product was then extracted (CH_2Cl_2) and dried (Na_2SO_4). After concentration, the product was purified by column chromatography (CH_2Cl_2) to produce the acetylenic alcohol **15d** as an oil (1.5 g, 53% yield): R_f = 0.31 in CH_2Cl_2; IR ($CHCl_3$) 3400, 1778, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67–7.25 (20 H, m), 5.73 (1 H, s), 5.22 (2 H, s), 4.59 (1 H, s), 3.49 (1 H, s), 1.60 (3 H, s), 1.45 (3 H, s).

Benzyl 6α-[(Triphenylsilyl)ethynyl]-6β-(trifluoromethanesulfonato)penicillinate (16d). This compound was prepared as described for **10b** (yield = 74%): R_f = 0.50 in CH_2Cl_2; IR ($CHCl_3$) 1798, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68–7.20 (20 H, m), 5.81 (1 H, s), 5.19 (2 H, bs), 4.62 (1 H, s), 1.60 (3 H, s), 1.38 (3 H, s).

Allyl 6α-[3′-[(*tert*-Butyldimethylsilyl)oxy]propynyl]-6β-hydroxypenicillinate (17b). This compound was prepared as described for **9b** by using the (*tert*-butyldimethylsilyl)propargylic alcohol (yield = 28%): R_f = 0.26 in 2% EtOAc in CH_2Cl_2; ^1H NMR ($CDCl_3$) δ 5.90 (1 H, m), 5.63 (1 H, s), 5.36 (2 H, m), 4.70 (2 H, m), 4.55 (1 H, s), 4.42 (2 H, s), 1.61 (3 H, s), 1.53 (3 H, s), 0.92 (9 H, s), 0.14 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 170.1, 166.8, 130.9, 119.6, 87.9, 78.7, 78.0, 76.4, 69.4, 66.1, 64.1, 51.5, 33.3, 25.8, 25.6, 18.1, 5.0, −5.3.

Benzhydryl 6α-[3′-[(*tert*-Butyldimethylsilyl)oxy]propynyl]-6β-hydroxypenicillinate (17c). This compound was prepared as described for **9b** by using the (*tert*-butyldimethylsilyl)propargylic alcohol (yield = 22%): R_f = 0.19 in CH_2Cl_2; IR ($CHCl_3$) 3400, 1780, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48–7.33 (10 H, m), 6.96 (1 H, s), 5.65 (1 H, s), 4.63 (1 H, s), 4.41 (2 H, s), 3.50 (1 H, bs), 1.59 (3 H, s), 1.32 (3 H, s), 0.91 (9 H, s), 0.13 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 166.2 (s), 138.9 (s), 128.5, 128.3, 128.2, 127.4, 126.9, 88.2 (s), 78.6, 78.5, 78.2, 78.1, 76.8, 69.5 (d), 64.5 (s), 51.6 (t), 33.6 (q), 25.7 (q), 18.2 (s), −5.2 (q).

Allyl 6α-[3′-[(*tert*-Butyldimethylsilyl)oxy]propynyl]-6β-(trifluoromethanesulfonato)penicillinate (18b). This compound was prepared as described for **10b** (yield = 22%): R_f = 0.80 in CH_2Cl_2; IR (CCl_4) 1798 (s), 1738 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90 (1 H, m), 5.71 (1 H, s), 5.35 (2 H, m), 4.70 (2 H, m), 4.68 (1 H, s), 4.63 (2 H, s), 1.61 (3 H, s), 1.50 (3 H, s), 0.90 (9 H, s), 0.12 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 166.1, 161.5, 130.8, 119.9, 94.8, 88.1, 75.5, 73.4, 70.3, 66.3, 64.3, 51.4, 33.3, 25.6, 25.1, 18.1, −5.4.

Benzhydryl 6α-[3′-[(*tert*-Butyldimethylsilyl)oxy]propynyl]-6β-(trifluoromethanesulfonato)penicillinate (18c). This compound was prepared as described for **10b** (yield = 87%): R_f = 0.83 in CH_2Cl_2; IR ($CHCl_3$) 1795, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (10 H, m), 6.96 (1 H, s), 5.78 (1 H, s), 4.70 (1 H, s), 4.45 (2 H, s), 1.62 (3 H, s), 1.31 (3 H, s), 0.93 (9 H, s), 0.12 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 165.4 (s), 161.4 (s), 138.7 (s), 128.5, 128.3, 128.2, 127.9, 127.3, 127.0, 126.8, 117.8 (q, CF_3, J = 321.5), 94.8 (s), 88.1 (s), 78.7 (d), 75.6 (d), 73.3 (s), 70.3 (d), 64.5 (s), 51.2 (t), 33.2 (q), 25.5 (q), 24.7 (q), 18.0 (s), −5.5 (q).

Allyl 6α-(3′,3′-Diethoxypropynyl)-6β-hydroxypenicillinate (19b). This compound was prepared as described for **9b** (yield = 18%): R_f = 0.18 in CH_2Cl_2; IR ($CHCl_3$) 3400, 1780, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.08–5.82 (1 H, m), 5.64 (1 H, s), 5.49–5.20 (3 H, m), 4.80–4.60 (2 H, m), 4.53 (1 H, s), 3.70 (2 H, q, J = 7.0), 3.63 (2 H, q, J = 7.0), 1.60 (3 H, s), 1.52 (3 H, s), 1.24 (6 H, t, J = 7.0); ^{13}C NMR ($CDCl_3$) δ 169.6 (s), 166.8 (s), 131.0 (d), 119.4 (t), 90.9 (d), 83.9 (s), 79.9 (s), 77.7 (s), 76.0 (d), 69.3 (d), 65.9 (t), 63.6 (s), 60.9 (t), 32.8 (q), 25.7 (q), 14.8 (q).

Allyl 6α-(3′,3′-Diethoxypropynyl)-6β-(trifluoromethanesulfonato)penicillinate (20b). This compound was prepared as described for **10b** (yield = 45%): R_f = 0.77 in CH_2Cl_2; IR ($CHCl_3$) 1796, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.08–5.78 (1 H, m), 5.69 (1 H, s), 5.40–5.20 (3 H, m), 4.61–4.50 (3 H, m), 3.62 (2 H, q, J = 7.0), 3.53 (2 H, q, J = 7.0), 2.04 (3 H, s), 1.89 (3 H, s), 1.10 (6 H, t, J = 7.0); ^{13}C NMR ($CDCl_3$) δ 165.9 (s), 161.0 (s), 130.7 (d), 119.8 (t), 117.6 (CF_3, q, J = 320.6), 91.0 (s), 90.9 (d), 87.7 (s), 75.3 (d), 73.2 (s), 70.2 (d), 66.2 (t), 64.2 (s), 61.3 (t), 61.2 (t), 33.1 (q), 24.9 (q), 14.7 (q).

Allyl 6α-(Carbethoxyethynyl)-6β-hydroxypenicillinate (21b). This compound was prepared as described for **9b** (yield = 28%): R_f = 0.20 in 2% EtOAc in CH_2Cl_2; IR ($CHCl_3$) 3400, 1782, 1738, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.04–5.86 (1 H, m), 5.69 (1 H, s), 5.47–5.20 (2 H, m), 4.71–4.64 (2 H, m), 4.55 (1 H, s), 4.27 (2 H, q, J = 7.0), 3.84 (1 H, bs), 1.60 (3 H, s), 1.52 (3 H, s), 1.32 (3 H, t, J = 7.0); ^{13}C NMR ($CDCl_3$) δ 168.0 (s), 166.5 (s), 152.4 (s), 130.8 (d), 120.0 (t), 79.8 (s), 79.5 (s), 77.8 (s), 76.0 (d), 69.5 (d), 66.3 (t), 64.5 (s), 62.5 (t), 33.5 (q), 25.7 (q), 13.9 (q).

Allyl 6α-(Carbethoxyethynyl)-6β-(trifluoromethanesulfonato)penicillinate (22b). This compound was prepared as described for **10b** (yield = 77%): R_f = 0.84 in CH_2Cl_2; IR ($CHCl_3$) 1800, 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.10–5.83 (1 H, m), 5.80 (1 H, s), 5.50–5.29 (2 H, m), 4.81–4.60 (3 H, m), 4.31 (2 H, q, J = 7.1), 1.64 (3 H, s), 1.53 (3 H, s), 1.35 (3 H, t, J = 7.1); ^{13}C NMR ($CDCl_3$) δ 165.8 (s), 159.8 (s), 151.5 (s), 130.6 (d), 120.2 (t), 117.8 (CF_3, q, J = 321.4), 87.2 (s), 84.8 (s), 75.1 (d), 73.4 (s), 70.5 (d), 66.5 (t), 64.5 (s), 63.0 (t), 33.3 (q), 25.0 (q), 13.8 (q).

Benzhydryl 6α-[3′-[(*tert*-Butyldimethylsilyl)oxy]-3′-phenylpropynyl]-6β-hydroxypenicillinate (23c). This compound was prepared as described for **9b** except that the reaction mixture was allowed to warm before quenching (yield = 16%): R_f = 0.28 in CH_2Cl_2; IR ($CDCl_3$) 3400, 1780, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.17 (15 H, m), 6.96 (1 H, s), 5.63 (1 H, s), 5.60 (1 H, s), 4.62 (1 H, s), 3.49 (1 H, bs), 1.59 (3 H, s), 1.31 (3 H, s), 0.94 (9 H, s), 0.18 (3 H, s), 0.15 (3 H, s).

Benzhydryl 6α-[3′-[(*tert*-Butyldimethylsilyl)oxy]-3′-phenylpropynyl]-6β-(trifluoromethanesulfonato)penicillinate (24c). This compound was prepared as described for **10b** (yield = 33%): R_f = 0.89 in CH_2Cl_2; IR ($CDCl_3$) 2950, 1800, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.28 (15 H, m), 6.95 (1 H, s), 5.73 (1 H, s), 5.61 (1 H, s), 4.70 (1 H, s), 1.62 (3 H, s), 1.30 (3 H, s), 0.93 (9 H, s), 0.17 (3 H, s), 0.12 (3 H, s).

Benzhydryl 6α-[3′-(2″-Oxopyrrolidyl)propynyl]-6β-hydroxypenicillinate (25c). This compound was prepared as described for **9b** except that the reaction was allowed to warm before quenching (yield = 37%): R_f = 0.35 in 1:1 CH_2Cl_2/EtOAc; IR (CCl_4) 1795, 1750, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (5 H, s), 7.35 (5 H, s), 6.95 (1 H, s), 5.60 (1 H, s), 4.61 (1 H, s), 4.39 (1 H, bs), 4.21 (2 H, s), 3.47 (2 H, m), 2.41 (2 H, m), 2.05 (2 H, m), 1.59 (3 H, s), 1.30 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 174.7 (s), 170.1 (ss), 166.2 (s), 138.7 (s), 128.2, 128.1, 127.9, 127.1, 126.6, 82.5 (s), 78.9 (s), 78.1 (d), 77.6 (s), 76.1 (d), 69.1 (d), 63.7 (s), 46.2 (t), 32.7 (q), 31.9 (t), 30.2 (t), 25.3 (q), 17.1 (t).

Benzhydryl 6α-[3′-(2″-Oxopyrrolidyl)propynyl]-6β-(trifluoromethanesulfonato)penicillinate (26c). This compound was prepared as described for **10b** (yield = 64%): R_f = 0.63 in 3:1 CH_2Cl_2/EtOAc; IR (Nujol mull) 2244, 1802, 1745, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (5 H, s), 7.36 (5 H, s), 6.96 (1 H, s), 5.72 (1 H, s), 4.71 (1 H, s), 4.29 (2 H, s), 3.46 (2 H, m), 2.42 (2 H, m), 2.09 (2 H, m), 1.61 (3 H, s), 1.31 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 174.3 (s), 165.4 (s), 161.2 (s), 138.6 (s), 128.9, 128.5, 128.2, 127.3, 126.8, 117.9 (q, CF_3, J = 321.0), 90.6 (s), 87.8 (s), 78.7 (d), 75.5 (d), 72.6 (s), 70.2 (d), 64.5 (s), 46.0 (t), 33.2 (q), 31.9 (t), 30.1 (t), 24.7 (q), 17.4 (t).

Allyl 6-(α-Iodovinylidene)penicillinate (27b). Copper(I) iodide (CuI, 23 mg, 0.12 mmol) was added in one portion to a solution of triflate **10b** (41 mg, 0.10 mmol) in DMF (0.5 mL) at rt. The solution was stirred in the dark for 0.5 h. The DMF was removed in vacuo at rt. The remaining oil was dissolved (ether), washed (water), dried (Na_2SO_4), and concentrated to leave a dark gum. This material was purified by column chromatography (1:1 CH_2Cl_2/hexane) to yield the desired iodoallene **27b** as a reddish oil (15 mg, 38%): R_f = 0.42 in CH_2Cl_2; IR ($CHCl_3$) 1950,

1758, 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.57 (1 H, s), 6.05–5.85 (1 H, m), 5.96 (1 H, s), 5.50–5.30 (2 H, m), 4.75–4.65 (2 H, m), 4.55 (1 H, s), 1.64 (3 H, s), 1.50 (3 H, s); high-resolution mass spectrum m/z calcd for $C_{13}H_{14}INO_3S$ 390.9739, found 390.9741.

Benzhydryl 6-(α-Iodovinylidene)penicillinate (27c). This compound was prepared as described for **27b** (yield = 47%): R_f = 0.56 in CH_2Cl_2; IR ($CHCl_3$) 1950, 1770, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (10 H, bs), 6.96 (1 H, s), 6.58 (1 H, d, J = 1.3), 5.97 (1 H, d, J = 1.3), 4.63 (1 H, s), 1.62 (3 H, s), 1.29 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 194.8 (s), 166.5 (s), 165.4 (s), 138.9 (s), 128.4, 128.2, 128.0, 127.3, 126.9, 110.8 (s), 78.2 (d), 70.1 (d), 67.2 (d), 65.0 (s), 44.0 (d), 33.5 (q), 25.3 (q).

Benzyl 6-(α-Iodovinylidene)penicillinate (27d). This compound was prepared as described for **27b** (yield 50%): R_f = 0.53 in CH_2Cl_2; IR ($CDCl_3$) 1958, 1778, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (5 H, bs), 6.56 (1 H, d, J = 1.3), 5.94 (1 H, d, J = 1.3), 5.21 (2 H, s), 4.56 (1 H, s), 1.61 (3 H, s), 1.42 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 195.0, 167.4, 165.5, 134.8, 128.7, 110.8, 70.3, 67.4, 67.1, 65.1, 43.6, 33.3, 25.8; high-resolution mass spectrum m/z calcd for $C_{17}H_{16}INO_3S$ 440.9897, found 440.9907. Anal. Calcd for $C_{17}H_{16}INO_3S$: C, 46.27; H, 3.65; N, 3.17; I, 28.76. Found: C, 45.86; H, 3.71; N, 3.12; I, 27.52.

Allyl 6α-(Bromovinylidene)penicillinate (28b). This compound was prepared by using CuBr/DMF with triflate **10b** as described for **27b** (yield = 78%): R_f = 0.50 in CH_2Cl_2; IR ($CHCl_3$) 1762, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.62 (1 H, s), 5.90 (1 H, s), 6.05–5.85 (1 H, m), 5.50–5.20 (2 H, m), 4.75–4.65 (2 H, m), 4.57 (1 H, s), 1.63 (3 H, s), 1.50 (3 H, s); high-resolution mass spectrum m/z calcd for $C_{13}H_{14}{}^{79}BrNO_3S$ 343.9956, found 343.9951.

Benzhydryl 6α-(Bromovinylidene)penicillinate (28c). This compound was prepared as described for **27b** (yield = 30%): R_f = 0.50 in CH_2Cl_2; IR ($CDCl_3$) 1770, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (5 H, bs), 7.36 (5 H, bs), 6.96 (1 H, s), 6.62 (1 H, s), 5.97 (1 H, s), 4.64 (1 H, s), 1.61 (3 H, s), 1.29 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 194.0, 166.6, 165.3, 139.1, 130.0, 128.6, 128.4, 128.3, 127.5, 127.1, 114.8, 80.6, 78.5, 70.5, 68.0, 65.2, 33.7, 25.4; high-resolution mass spectrum m/z calcd for $C_{23}H_{20}{}^{79}BrNO_3S$ 469.0347, found 469.0345.

Benzyl 6α-(Bromovinylidene)penicillinate (28d). This compound was prepared as described for **27b** (yield = 41%): R_f = 0.58 in CH_2Cl_2; IR ($CHCl_3$) 1765, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (5 H, bs), 6.62 (1 H, s), 5.94 (1 H, s), 5.21 (2 H, s), 4.58 (1 H, s), 1.61 (3 H, s), 1.42 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 193.9, 167.3, 165.0, 134.8, 128.7, 114.6, 80.4, 70.4, 67.8, 67.4, 65.1, 33.4, 25.7; high-resolution mass spectrum m/z calcd for $C_{17}H_{16}{}^{79}BrNO_3S$ 393.0034, found 393.0023.

Allyl 6-(α-Iodo-β-methylvinylidene)penicillinate (29b). This compound was prepared by using CuI/DMF with triflate **12b** as described for **27b** (yield = 42%, a single isomer): R_f = 0.40 in CH_2Cl_2; IR ($CHCl_3$) 1950, 1760, 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.0–5.70 (1 H, m), 5.78 (1 H, s), 5.40–5.18 (2 H, m), 4.66–4.56 (2 H, m), 4.46 (1 H, s), 2.46 (3 H, s), 1.56 (3 H, s), 1.42 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 192.6 (s), 167.1 (s), 166.4 (s), 130.9 (d), 119.3 (t), 107.1 (s), 70.0 (d), 67.2 (d), 65.8 (t), 64.8 (s), 62.7 (s), 32.7 (q), 27.6 (q), 25.8 (q); high-resolution mass spectrum m/z calcd for $C_{14}H_{16}INO_3S$ 404.9896, found 404.9886.

Allyl 6-(Methylbromovinylidene)penicillinate (Mixture of Diasteriomers) (30b). Lithium bromide (LiBr, 130 mg, 1.5 mmol) and copper(I) bromide (CuBr, 215 mg, 1.5 mmol) were added in one portion to a solution of triflate **12b** (427 mg, 1.0 mmol) in anhydrous THF (30 mL). The mixture was allowed to stir at rt for 1 h. The THF was removed in vacuo. The residue was dissolved (ether), washed (water), dried (Na_2SO_4), and concentrated in vacuo. The product was purified by column chromatography (1:1 CH_2Cl_2/hexane) to give a 1:1 mixture of diasteriomers (yield = 95%): R_f = 0.49 in CH_2Cl_2; IR ($CHCl_3$) 1960, 1765, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.93–5.70 (1 H, m), 5.75 (1 H, s), 5.32–5.10 (2 H, m), 4.61–4.49 (2 H, m), 4.35 (1 H, s), 2.26 (3 H, s), 1.49 (3 H, s), 1.35 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 192.1 (s), 167.1 (s), 166.0 (s), 131.1 (d), 119.4 (t), 111.4 and 111.2 (s), 96.0 (s), 70.3 (d), 68.3 and 67.9 (d), 65.9 (t), 64.9 and 64.7 (s), 33.0 (q), 25.7 (q), 24.7 (q); high-resolution mass spectrum m/z calcd for $C_{14}H_{16}{}^{79}BrNO_3S$ 357.0034, found 357.0033.

Allyl 6-[Iodo[[(*tert*-butyldimethylsilyl)oxy]methyl]vinylidene]penicillinate (Mixture of Diasteriomers) (31b). This compound was prepared by using the CuI/LiI/THF method with triflate **18b**. The product was purified by column chromatography (1:1 hexane/CH_2Cl_2) to give a 1:1 mixture of diasteriomers (yield = 89%): R_f = 0.33 in CH_2Cl_2; IR ($CHCl_3$) 1950, 1760, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.93 (1 H, m), 5.92 (1 H, s), 5.38 (2 H, m), 4.70 (2 H, m), 4.53 (1 H, s), 4.31 (2 H, s), 1.64 (3 H, s), 1.50 (3 H, s), 0.88 (9 H, s), 0.14 (3 H, s), 0.11 (3 H, s).

Benzhydryl 6-[Iodo[[(*tert*-butyldimethylsilyl)oxy]methyl]vinylidene]penicillinate (Mixture of Diasteriomers) (31c). This compound was prepared by using the CuI/LiI/THF method with triflate **18c**. The product was purified by column chromatography (CH_2Cl_2) to give a 1:1 mixture of diasteriomers (yield = 42%): R_f = 0.53 in CH_2Cl_2; IR ($CHCl_3$) 1950, 1760, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (10 H, bs), 6.96 (1 H, s), 5.91 (1 H, s), 4.61 (1 H, s), 4.31 (2 H, s), 1.62 (3 H, s), 1.28 (3 H, s), 0.93 (9 H, s), 0.14 (3 H, s), 0.13 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 192.4 and 192.0 (s), 166.8 (s), 166.2 (s), 139.1 (s), 130.0, 129.8, 128.5, 128.3, 128.1, 127.5, 127.0, 111.1 and 110.8 (s), 78.3 (d), 72.0, 71.4, 70.3, 68.5, 67.7, 67.3, 65.7, 65.2, 64.6, 33.6 and 33.4 (q), 25.8 and 25.6 (q), 25.3 (q), 18.3 and 18.2 (s), -5.2 (q).

Allyl 6-[(Diethoxymethyl)iodovinylidene]penicillinate (Mixture of Diasteriomers) (32b). This compound was prepared by using the CuI/LiI/THF method with the triflate **20b**. The product was purified by column chromatography (CH_2Cl_2) to give a 1:1 mixture of diasteriomers (yield = 58%): R_f = 0.69 in CH_2Cl_2; IR ($CHCl_3$) 1950, 1760, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.09–5.81 (2 H, m), 5.49–5.20 (2 H, m), 4.82–4.60 (3 H, m), 4.54 (1 H, s), 3.85–3.44 (4 H, m), 1.63 (3 H, bs), 1.49 (3 H, bs), 1.38–1.09 (3 H, m); ^{13}C NMR δ 193.3 (s), 167.1 (s), 165.5 (s), 131.1 (d), 119.5 (t), 110.4 and 110.2 (s), 100.8 and 100.7 (d), 70.3 (s), 70.2 (d), 69.9 and 69.6 (s), 68.1 (d), 67.4 (s), 66.0 (d), 64.7 and 64.5 (s), 62.2 and 62.1 (t), 61.9 (s), 52.6 (t), 33.2 and 33.0 (q), 25.7 (q), 22.4 (q), 14.8 (q); high-resolution mass spectrum m/z calcd for $C_{18}H_{24}INO_5S$ 493.0420, found 493.0431.

Allyl 6-(Carbethoxyiodovinylidene)penicillinate (Mixture of Diasteriomers) (33b). This compound was prepared by using the CuI/LiI/THF method with the triflate **22b**. The product was purified by column chromatography (CH_2Cl_2) to give a 1:1 mixture of diasteriomers (yield = 40%): R_f = 0.56 in CH_2Cl_2; IR ($CHCl_3$) 1950, 1782, 1727, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.10–5.76 (2 H, m), 5.49–5.22 (2 H, m), 4.77–4.50 (3 H, m), 4.40–4.09 (2 H, m), 1.61 (3 H, bs), 1.49 (3 H, bs), 1.45–1.10 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 201.12 and 201.09, 167.1, 163.7, 160.2, 131.0, 119.8, 110.8 and 110.4, 70.5 and 70.4, 68.2, 67.6, 66.2, 66.0 and 65.9, 65.2, 64.8 and 64.7, 64.0 and 63.8, 33.4 and 33.1, 25.6, 14.1 and 14.0.

Benzhydryl 6-[[[(*tert*-Butyldimethylsilyl)oxy]phenylmethyl]iodovinylidene]penicillinate (Mixture of Diasteriomers) (34c). This compound was prepared as described for **27b** (yield = 68%): R_f = 0.78 in CH_2Cl_2; IR ($CDCl_3$) 1942, 1765, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (15 H, m), 6.97 and 6.95 (1 H, s), 5.91 and 5.88 (1 H, s), 5.12 and 5.05 (1 H, s), 4.62 (1 H, s), 1.58 and 1.54 (3 H, s), 1.28 (3 H, s), 0.97 and 0.96 (9 H, s), 0.23 and 0.20 (3 H, s), 0.06 and 0.05 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 192.5 and 192.3 (s), 166.8 and 166.7 (s), 166.0 (s), 140.7 and 140.5 (s), 139.3, 128.7, 128.6, 128.4, 128.3, 127.6, 127.2, 126.5, 110.2 and 110.1 (s), 79.6 and 79.1 (s), 78.4 (d), 76.8, 76.3, 70.5 (d), 67.8 and 67.6 (d), 65.3 and 65.0 (s), 34.0 and 33.6 (q), 26.0 and 25.7 and 25.5 (q), 18.4 (s), -4.4 and -4.7 and -4.9 (q); high-resolution mass spectrum m/z calcd for $C_{36}H_{40}INO_4SiS$ 737.1473, found 737.1483.

Allyl 6-(α-*tert*-Butylvinylidene)penicillinate (35b). To a suspension of CuCN (61.8 mg, 0.69 mmol) in THF (3 mL) at -78 °C was added *t*-BuLi (0.705 mL, 1.2 mmol). The cooling bath was removed until all the solid had dissolved. This solution was again cooled to -78 °C, and then it was cannulated into a solution of the triflate **10b** (247.8 mg, 0.6 mmol) in THF (6 mL) at -78 °C. The solution was stirred for 1 min before quenching with saturated NH_4Cl (5 mL). The mixture was extracted with ether (50 mL), dried (Na_2SO_4), concentrated, and chromatographed (CH_2Cl_2) to give **35b** as a pale yellow semisolid (90 mg, 47% yield): R_f = 0.56 in CH_2Cl_2; IR ($CDCl_3$) 1960, 1760, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.02–5.84 (1 H, m), 5.86 (1 H, s), 5.85 (1 H, s), 5.45–5.28 (2 H, m), 4.71–4.66 (2 H, m), 4.53 (1 H, s), 1.64 (3 H, s), 1.49 (3 H, s), 1.13 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 193.91 (s), 168.5 (s), 167.4 (s), 131.1 (d), 119.1 (t), 111.7 (d), 109.8 (s), 69.8 (d), 68.6 (d), 65.7 (t), 64.5 (s), 33.3 (s), 32.6 (q), 29.6 (q), 25.9 (q); high-resolution mass spectrum m/z calcd for $C_{17}H_{23}NO_3S$ 321.1399, found 321.1397.

Benzhydryl 6-(α-*tert*-Butylvinylidene)penicillinate (35c). This compound was prepared as described for **35b** (yield = 38%): R_f = 0.41 in CH_2Cl_2; IR ($CHCl_3$) 2960, 1970, 1760, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37 (10 H, bs), 6.96 (1 H, s), 5.87 (1 H, s), 5.86 (1 H, s), 4.62 (1 H, s), 1.62 (3 H, s), 1.28 (3 H, s), 1.14 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 194.0 (s), 168.6 (s), 166.9 (s), 139.1 (s), 128.3, 128.1, 127.9, 127.3, 126.8, 111.8 (d), 110.1 (s), 78.0 (d), 70.0 (d), 68.9 (d), 64.7 (s), 33.3 (s), 33.1 (q), 29.6 (q), 25.5 (q); high-resolution mass spectrum *m/z* calcd for $C_{27}H_{29}NO_3S$ 447.1868, found 447.1866.

Benzyl 6-(α-*tert*-Butylvinylidene)penicillinate (35d). This compound was prepared as described in **35b** (yield = 60%): R_f = 0.45 in 1:1 CH_2Cl_2/hexane; IR ($CDCl_3$) 1965, 1760, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (5 H, bs), 5.87 (1 H, d, *J* = 1.5), 5.84 (1 H, d, *J* = 1.5), 5.22 (2 H, bs), 4.54 (1 H, s), 1.61 (3 H, s), 1.42 (3 H, s), 1.13 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 194.2, 169.0, 168.0, 134.9, 128.6, 128.5, 112.0, 110.0, 70.1, 68.9, 67.3, 64.8, 33.5, 32.9, 29.8, 26.0; high-resolution mass spectrum *m/z* calcd for $C_{21}H_{25}NO_3S$ 371.1557, found 371.1569. Anal. Calcd for $C_{21}H_{25}NO_3S$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.39; H, 6.63; N, 3.71.

Allyl 6-(α-Methylvinylidene)penicillinate (36b). Methyllithium (0.14 mL, 1.4 M in ether, 0.2 mmol) was added to a cold (−78 °C) suspension of CuCN (11 mg, 0.12 mmol) in anhydrous THF (1 mL). The cooling bath was temporarily removed, and the cold solution allowed to stir without external cooling until all the solid had gone into solution (~3 min). The reaction mixture was recooled to −78 °C, and this cold (−78 °C) cuprate solution was cannulated to a cold (−78 °C) solution of the triflate **10b** (41 mg, 0.1 mmol) in THF (2 mL). After being stirred for 1 min, the reaction mixture was quenched with cold saturated NH_4Cl solution, extracted (ether), dried (Na_2SO_4), concentrated, and purified by column chromatography to yield **36b** (20 mg, 72% yield): R_f = 0.49 in CH_2Cl_2; IR ($CHCl_3$) 1958, 1759, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05–5.80 (2 H, m), 5.85 (1 H, s), 5.50–5.30 (2 H, m), 4.70–4.65 (2 H, m), 4.53 (1 H, s), 1.85 (3 H, d, *J* = 7.5), 1.63 (3 H, s), 1.49 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 197.1 (s), 169.0 (s), 167.7 (s), 131.2 (d), 119.4 (t), 108.0 (s), 95.6 (d), 70.1 (d), 68.7 (d), 66.0 (t), 64.8 (s), 33.1 (q), 26.1 (q), 13.6 (q); high-resolution mass spectrum *m/z* calcd for $C_{14}H_{17}NO_3S$ 279.0929, found 279.0935.

Benzhydryl 6-(α-Methylvinylidene)penicillinate (36c). This compound was prepared as described for **36b** (yield = 30%): R_f = 0.44 in CH_2Cl_2; IR ($CDCl_3$) 1960, 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (10 H, bs), 6.98 (1 H, s), 5.87 (1 H, s), 5.84 (1 H, q, *J* = 7.5), 4.62 (1 H, s), 1.82 (3 H, d, *J* = 7.5), 1.60 (3 H, s), 1.21 (3 H, s); high-resolution mass spectrum *m/z* calcd for $C_{24}H_{23}NO_3S$ 405.1399, found 405.1394.

Benzyl 6-(α-Methylvinylidene)penicillinate (36d). This compound was prepared as described for **36b** (yield = 60%): R_f = 0.51 in CH_2Cl_2; ^1H NMR ($CDCl_3$) δ 7.39 (5 H, bs), 5.85 (1 H, q, *J* = 7.4), 5.84 (1 H, s), 5.21 (2 H, s), 4.54 (1 H, s), 1.85 (3 H, d, *J* = 7.4), 1.60 (3 H, s), 1.41 (3 H, s).

Benzyl 6-(α-Phenylvinylidene)penicillinate (37d). This compound was prepared as described for **36b** by adding $Ph_2CuCNLi_2$ to the triflate **10d** with the exception that the triflate solution was cooled to −100 °C (yield = 54%): R_f = 0.47 in CH_2Cl_2; IR ($CDCl_3$) 1950, 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (5 H, bs), 7.35 (5 H, bs), 6.83 (1 H, d, *J* = 1.5), 5.99 (1 H, d, *J* = 1.5), 5.24 (2 H, s), 4.61 (1 H, s), 1.66 (3 H, s), 1.45 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 198.2, 167.8, 165.5, 130.8, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 111.5, 102.9, 70.2, 69.0, 67.4, 65.1, 33.1, 26.0; high-resolution mass spectrum *m/z* calcd for $C_{23}H_{21}NO_3S$ 391.1243, found 391.1253.

Allyl 6-[α-(2′-Methoxyphenyl)vinylidene]penicillinate (38b). This compound was prepared by adding $(2\text{-MeOPh})_2CuCNLi_2$ to triflate **10b** as described for **36b** (yield = 49%): R_f = 0.68 in CH_2Cl_2; IR ($CDCl_3$) 1938, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (2 H, m), 7.19 (1 H, d, *J* = 1.5), 6.95 (2 H, m), 5.96 (1 H, d, *J* = 1.5), 5.94 (1 H, m), 5.41 (2 H, m), 4.72 (2 H, m), 4.58 (1 H, s), 3.86 (3 H, s), 1.69 (3 H, s), 1.52 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 199.5 (s), 168.4 (s), 167.8 (s), 156.7 (s), 131.2 (d), 130.1 (d), 129.3 (d), 120.9 (d), 119.5 (t), 119.3 (s), 111.1 (d), 110.3 (s), 97.3 (d), 70.2 (d), 69.2 (d), 66.1 (t), 64.8 (s), 55.6 (q), 33.3 (q), 26.0 (q); high-resolution mass spectrum *m/z* calcd for $C_{20}H_{21}NO_4S$ 371.1190, found 371.1189.

Allyl 6-[α-*tert*-Butyl-β-[(*p*-chlorophenyl)sulfenyl]vinylidene]penicillinate (39b). This compound was prepared by the addition of $(t\text{-Bu})_2CuCNLi_2$ to mesylate **14b** (yield = 64%) as described above for **36b** to produce a white solid (mp = 163–164 °C): R_f = 0.64 in CH_2Cl_2; IR ($CDCl_3$) 1950, 1750, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.23 (4 H, ABq, *J* = 8.5 Hz), 6.00–5.70 (1 H, m), 5.62 (1 H, s), 5.40–5.20 (2 H, m), 4.62–4.58 (2 H, m), 4.31 (1 H, s), 1.36 (3 H, s), 1.30 (3 H, s), 1.25 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 189.9, 167.9, 135.8, 134.9, 131.1, 129.7, 129.6, 128.9, 119.4, 113.1, 69.9, 68.8, 65.9, 64.5, 37.0, 32.5, 29.6, 26.0; high-resolution mass spectrum *m/z* calcd for $C_{23}H_{26}{}^{35}ClNO_3S_2$: 463.1042, found 463.1042.

Benzyl 6-[α-Methyl-β-(triphenylsilyl)vinylidene]penicillinate (40d). This compound was prepared by the addition of $Me_2CuCNLi_2$ to triflate **16d** as described for **36b** (yield = 50%): R_f = 0.36 in CH_2Cl_2; IR ($CDCl_3$) 1940, 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.55 (20 H, m), 5.84 (1 H, s), 5.18 (2 H, s), 4.34 (1 H, s), 1.93 (3 H, s), 1.28 (3 H, s), 1.07 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 196.6 (s), 169.7 (s), 168.1 (s), 136.2–127.8 (aromatic), 103.8 (s), 98.3 (s), 69.7 (d), 68.9 (d), 67.1 (t), 64.2 (s), 32.8 (q), 25.7 (q), 17.2 (q); high-resolution mass spectrum *m/z* calcd for $C_{36}H_{33}NO_3SiS$ 587.1952, found 587.1942.

Allyl 6-(Dimethylvinylidene)penicillinate (41b). This compound was prepared by the addition of $Me_2CuCNLi_2$ to triflate **12b** as described for **36b** (yield = 44%): R_f = 0.82 in CH_2Cl_2; IR ($CDCl_3$) 1960, 1758, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05–5.80 (1 H, m), 5.78 (1 H, s), 5.50–5.21 (2 H, m), 4.80–4.73 (2 H, m), 4.68 (1 H, s), 1.86 (3 H, s), 1.85 (3 H, s), 1.63 (3 H, s), 1.48 (3 H, s).

Allyl 6-(α-Phenyl-β-methylvinylidene)penicillinate (42b). This compound was prepared by adding $Ph_2CuCNLi_2$ to triflate **12b** as described for **36b** (yield = 59%): R_f = 0.62 in CH_2Cl_2; IR ($CDCl_3$) 1940, 1735, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49–7.30 (5 H, m), 6.08–5.83 (1 H, m), 5.93 (1 H, s), 5.49–5.25 (2 H, m), 4.70–4.62 (2 H, m), 4.58 (1 H, s), 2.25 (3 H, s), 1.68 (3 H, s), 1.51 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 197.9, 168.8, 167.7, 133.7, 131.2, 128.6, 128.5, 126.5, 119.5, 110.6, 109.4, 70.3, 69.0, 66.0, 64.9, 32.7, 26.1, 16.7; high-resolution mass spectrum *m/z* calcd for $C_{20}H_{21}NO_3S$ 355.1243, found 355.1243.

Allyl 6-(α-*tert*-Butyl-β-methylvinylidene)penicillinate (43b). This compound was prepared by adding $t\text{-Bu}_2CuCNLi_2$ to triflate **12b** as described for **36b** (yield = 80%): R_f = 0.62 in 1:1 CH_2Cl_2/hexane; IR ($CDCl_3$) 2960, 1955, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (1 H, m), 5.78 (1 H, s), 4.35 (2 H, m), 4.67 (2 H, m), 4.51 (1 H, s), 1.84 (3 H, s), 1.62 (3 H, s), 1.48 (3 H, s), 1.11 (9 H, s); high-resolution mass spectrum *m/z* calcd for $C_{18}H_{25}NO_3S$ 335.1555, found 335.1553.

Benzhydryl [α-Phenyl-β-[(2′-oxopyrrolidyl)methyl]vinylidene]penicillinate (44c). This compound was prepared by adding $Ph_2CuCNLi_2$ to triflate **26c** as described for **36b** (yield = 78%): R_f = 0.52 in 4:1 CH_2Cl_2/EtOAc; ^1H NMR ($CDCl_3$) δ 7.38 (15 H, bs), 6.99 (1 H, s), 5.97 (1 H, s), 4.67 (1 H, s), 4.65 (1 H, A of ABq, *J* = 15.5), 4.32 (1 H, B of ABq, *J* = 15.5), 3.45 (2 H, m), 2.43 (2 H, m), 2.05 (2 H, m), 1.68 (3 H, s), 1.31 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 196.7 (s), 174.8 (s), 167.7 (s), 166.8 (s), 139.0 (s), 131.0 (s), 128.9, 128.8, 128.5, 128.3, 128.1, 127.4, 126.9, 111.9 (s), 111.7 (s), 78.3 (d), 70.2 (d), 68.9 (d), 65.4 (s), 46.8 (t), 42.5 (t), 33.0 (q), 30.6 (t), 25.7 (q), 17.5 (t).

Benzhydryl [α-*tert*-Butyl-β-[(2′-oxopyrrolidyl)methyl]vinylidene]penicillinate (45c). This compound was prepared by adding $(t\text{-Bu})_2CuCNLi_2$ to triflate **26c** as described for **36b** (yield = 72%): R_f = 0.49 in 4:1 CH_2Cl_2/EtOAc; ^1H NMR ($CDCl_3$) δ 7.34 (10 H, m), 6.96 (1 H, s), 5.82 (1 H, s), 4.58 (1 H, s), 4.37 (1 H, A of ABq, *J* = 15.3), 3.73 (1 H, B of ABq, *J* = 15.3), 3.39 (2 H, m), 2.40 (2 H, m), 2.04 (2 H, m), 1.62 (3 H, s), 1.27 (3 H, s), 1.17 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 192.4 (s), 174.7 (s), 168.9 (s), 167.1 (s), 139.1 (s), 128.5, 128.3, 128.1, 127.5, 126.9, 120.6 (s), 111.2 (s), 78.2 (d), 70.1 (d), 68.9 (d), 65.3 (s), 46.9 (t), 40.7 (t), 34.7 (s), 32.6 (q), 30.7 (t), 28.9 (q), 25.9 (q), 17.6 (t).

Benzyhydryl 6-Vinylidenepenicillinate (46c). To a solution of the iodoallene **27c** (6.85 g, 13.2 mmol) in MeOH (90 mL) was added NH_4Cl (1.6 g, 30 mmol) and Zn–Cu couple (1.3 g, 20 mmol). After 1 h, the mixture was concentrated. The concentrate was dissolved in Et_2O (150 mL), washed with H_2O (10 mL), dried (Na_2SO_4), concentrated, and chromatographed (7:3 and 1:1 CH_2Cl_2/hexane) to give a white foamy solid (2.79 g, 54% yield): R_f

= 0.71 in CH_2Cl_2; IR ($CHCl_3$) 1970, 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (10 H, bs), 6.93 (1 H, s), 5.87 (1 H, t, J = 1.5), 5.42 (1 H, d, J = 1.5), 5.41 (1 H, d, J = 1.5), 4.59 (1 H, s), 1.60 (3 H, s), 1.25 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 199.5 (s), 168.0 (s), 166.9 (s), 139.2 (s), 139.1 (s), 128.5 (d), 128.3 (d), 128.1 (d), 127.5 (d), 127.0 (d), 108.6 (s), 83.8 (t), 70.1 (d), 68.7 (d), 65.0 (s), 33.6 (q), 25.5 (q).

Benzhydryl 6-α-Ethynylpenicillinate (47c). To solution of the iodoallene **27c** (84 mg, 0.16 mmol) in THF (1 mL) at −78 °C was added *t*-BuLi (0.1 mL, 0.17 mmol). The mixture was stirred for 10 min, and then AcOH (0.1 mL) was added. After 10 min, saturated NH_4Cl (5 mL) was added. The mixture was extracted (ether, 15 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude material was chromatographed (1:1 CH_2Cl_2/hexane), and **47c** was isolated as an oil (26 mg, 40% yield): R_f = 0.85 in CH_2Cl_2; IR ($CHCl_3$) 3300, 1780, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (10 H, br s), 6.96 (1 H, s), 5.35 (1 H, d, J = 1.0), 4.62 (1 H, s), 4.02 (1 H, m), 2.57 (1 H, d, J = 2.7), 1.62 (3 H, s), 1.30 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.8 (s), 166.4 (s), 139.1 (s), 128.6, 128.4, 128.2, 127.5, 127.1, 78.5 (d), 75.7 (d), 75.4 (s), 69.9 (d), 67.8 (d), 65.2 (s), 51.8 (d), 33.6 (q), 25.7 (q).

Benzhydryl 6-(β-Ethynyl)-6-(α-acetyl)penicillinate (48c). To a solution of the iodoallene **27c** (104 mg, 0.2 mmol) in THF (2 mL) was added *t*-BuLi (0.14 mL, 0.22 mmol). After 10 min, acetyl chloride (30 mL, 0.42 mmol) was added at −78 °C and the resulting solution stirred for 10 min. Then AcOH (2 drops) was added followed by addition of saturated NH_4Cl (5 mL). The reaction mixture was extracted with Et_2O (15 mL), dried (Na_2SO_4), concentrated, and chromatographed (CH_2Cl_2) to yield **48c** as a colorless oil (40 mg, 45% yield): R_f = 0.46 in CH_2Cl_2; IR ($CHCl_3$) 3300, 1780, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (10 H, br s), 6.94 (1 H, s), 5.88 (1 H, s), 4.58 (1 H, s), 2.89 (1 H, s), 2.52 (3 H, s), 1.66 (3 H, s), 1.29 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 196.0 (s), 166.0 (s), 165.5 (s), 139.2 (s), 128.6, 128.4, 128.3, 127.4, 127.2, 80.3 (d), 78.6 (d), 74.2 (s), 71.9 (s), 70.3 (d), 67.7 (d), 64.3 (s), 33.1 (q), 27.7 (q), 25.7 (q).

Benzhydryl 6-(β-Ethynyl)-6-[α-(4′-Methylbenzoyl)]penicillinate (49c). To a solution of the iodoallene **27c** (44 mg, 0.085 mmol) in THF (1 mL) was added *t*-BuLi (0.06 mL, 0.102 mmol) and the resulting solution stirred for 10 min at −78 °C. Then *p*-toluyl chloride (16 mL, 18.5 mg, 0.12 mmol) was added to the above reaction mixture, and it was further stirred for 25 min at −78 °C and quenched with saturated NH_4Cl (5 mL). The mixture was extracted with Et_2O (15 mL), dried (Na_2SO_4), concentrated in vacuo, and chromatographed (1:1 CH_2Cl_2/hexane) to yield **49c** as a colorless viscous oil (18 mg, 41%): R_f = 0.64 in CH_2Cl_2; IR ($CHCl_3$) 3300, 1780, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (2 H, d, J = 8.3), 7.36 (10 H, br, s), 7.35 (2 H, d, J = 8.3), 6.94 (1 H, s), 6.21 (1 H, s), 4.65 (1 H, s), 2.91 (1 H, s), 2.45 (3 H, s), 1.73 (3 H, s), 1.34 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 187.2 (s), 166.1 (s), 165.8 (s), 145.3 (s), 139.1 (s), 131.1, 130.7, 129.1, 128.6, 128.3, 128.2, 127.4, 127.1, 81.6 (d), 78.5 (d), 75.4 (s), 70.4 (d), 70.0 (s), 68.5 (d), 64.0 (s), 32.9 (q), 25.9 (q), 21.8 (q).

Benzhydryl 6-(β-Ethynyl)-6-[α-(4′-methoxybenzoyl)]penicillinate (50c). This compound was prepared as described for **49c** to give a viscous oil (yield = 27%): R_f = 0.45 in CH_2Cl_2; IR ($CHCl_3$) 3300, 1775, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.34 (2 H, d, J = 9.1), 7.36 (10 H, m), 7.00 (2 H, d, J = 9.1), 6.21 (1 H, s), 4.64 (1 H, s), 3.91 (3 H, s), 2.92 (1 H, s), 1.73 (3 H, s), 1.33 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 186.0 (s), 166.1, 164.4 (s), 139.2 (s), 133.1 (d), 128.6, 128.3, 128.2, 127.4, 127.1, 126.5, 113.7 (d), 81.4 (d), 78.5 (d), 75.6 (s), 70.4 (d), 69.7 (s), 68.5 (d), 64.0 (s), 55.5 (q), 32.8 (q), 25.9 (q).

Allyl 6-(Diethoxymethylvinylidene)penicillinate (Mixture of Diasteriomers) (52b). To a solution of the iodoallene **32b** (623 mg, 1.3 mmol) in THF (5 mL) at −78 °C was added EtMgBr (650 mL, 1.3 mmol). After 15 min, the reaction mixture was quenched with saturated NH_4Cl (5 mL), and extracted (Et_2O, 25 mL). The extract was washed (H_2O, 5 mL), dried (Na_4SO_4), concentrated, and chromatographed (1:1 CH_2Cl_2/hexane) to yield an off-white foamy solid **52b** (100 mg, 21% yield): R_f = 0.44 in CH_2Cl_2; IR ($CDCl_3$) 2975, 1965, 1755, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (1 H, m), 5.87 (1 H, s), 5.81 (1 H, d, J = 5.0), 5.33 (2 H, m), 5.12 (1 H, d, J = 5.0), 4.68 (2 H, d, J = 5.7), 4.54 (1 H, s), 3.57 (4 H, m), 1.65 (3 H, s), 1.49 (3 H, s), 1.24 (6 H, t, J = 7.0); ^{13}C NMR ($CDCl_3$) δ 195.7 (s), 167.6 (s), 131.2 (d), 119.5 (t), 110.5 (s), 99.4 (d), 98.9 (d), 70.2 (d), 68.6 (d), 66.0 (t), 64.7 (s), 61.7 (t), 33.2 (q), 23.9 (q), 15.0 (q); high-resolution mass spectrum m/z calcd for $C_{18}H_{25}NO_5S$ 367.1447, found 367.1450.

Allyl 6-(Carbethoxyvinylidene)penicillinate (Mixture of Diasteriomers) (53b). This compound was prepared from **33b** as described in **52b** (yield = 42%): R_f = 0.40 in CH_2Cl_2; IR ($CHCl_3$) 1970, 1770, 1740, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.15 and 6.12 (1 H, d, J = 1.4), 5.99 and 5.94 (1 H, d, J = 1.4), 6.10–5.80 (1 H, m), 5.50–5.20 (2 H, m), 4.75–4.60 (2 H, m), 4.69 and 4.66 (1 H, s), 4.23 (2 H, q, J = 7.1), 1.66 and 1.64 (3 H, s), 1.49 both isomers (3 H, s), 1.29 and 1.28 (3 H, t, J = 7.1); ^{13}C NMR ($CDCl_3$) δ 202.2 and 201.9 (s), 167.2 (s), 165.3 and 165.1 (s), 163.0 (s), 131.0 (d), 119.7 (t), 111.7 and 111.6 (s), 95.5 (d), 70.2 (d), 68.6 and 68.5 (d), 66.1 (t), 65.1 and 64.6 (s), 61.8 and 61.7 (t), 33.2 (q), 25.8 and 25.6 (q), 14.1 and 14.0 (q); high-resolution mass spectrum m/z calcd for $C_{16}H_{19}O_5NS$ 337.0985, found 337.0993.

Benzhydryl 6-Vinylidenepenicillinate *S,S*-Dioxide (54c). This compound was prepared from the sulfide **46c** in 16–20 h as described for **56d** (yield = 90%): R_f = 0.45 in CH_2Cl_2; IR ($CHCl_3$) 3300, 1980, 1790, 1750, 1335, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (5 H, s), 7.37 (5 H, s), 7.01 (1 H, s), 5.68 (2 H, m), 5.21 (1 H, t, J = 1.1), 4.55 (1 H, s), 1.61 (3 H, s), 1.13 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 202.2 (s), 167.0 (s), 166.0 (s), 138.9 (s), 138.6 (s), 128.8 (d), 128.7 (d), 128.3 (d), 127.6 (d), 126.8 (d), 98.8 (s), 85.8 (t), 79.1 (d), 69.1 (d), 64.2 (s), 63.3 (d), 19.7 (q), 18.7 (q); high-resolution mass spectrum m/z calcd for $C_{23}H_{21}NO_5S$ 423.1140, found 423.1128.

Allyl 6-(α-Methylvinylidene)penicillinate *S,S*-Dioxide (55b). This compound was prepared from the sulfide **36b** as described for **56d** (yield = 32%): R_f = 0.53 in CH_2Cl_2; ^1H NMR ($CDCl_3$) δ 6.13 (1 H, q, J = 7.5), 5.98 (1 H, m), 5.38 (2 H, m), 5.19 (1 H, s), 4.75 (2 H, m), 4.45 (1 H, s), 1.89 (3 H, d, J = 7.5), 1.63 (3 H, s), 1.45 (3 H, s); high-resolution mass spectrum m/z calcd for $C_{14}H_{17}NO_5S$ 311.0828, found 311.0822.

Benzyl 6-(α-Methylvinylidene)penicillinate *S,S*-Dioxide (55d). This compound was prepared from the sulfide **36d** as described in **56d** (yield = 62%): IR ($CHCl_3$) 1962, 1782, 1743, 1325, 1120 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.36 (5 H, br s), 6.05 (1 H, q, J = 7.5), 5.21 (2 H, ABq), 5.13 (1 H, s), 4.40 (1 H, s), 1.85 (3 H, d, J = 7.5), 1.52 (3 H, s), 1.27 (3 H, s).

Allyl 6-(α-*tert*-Butylvinylidene)penicillinate *S,S*-Dioxide (56b). This compound was prepared from the sulfide **35b** as described for **56d** (yield = 70%): R_f = 0.58 in CH_2Cl_2; IR ($CHCl_3$) 1960, 1780, 1740, 1320, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.07 (1 H, d, J = 1.5), 5.90 (1 H, m), 5.37 (2 H, m), 5.18 (1 H, d, J = 1.5), 4.70 (2 H, m), 4.40 (1 H, s), 1.57 (3 H, s), 1.41 (3 H, s), 1.12 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 197.5 (s), 167.9 (s), 166.8 (s), 130.7 (d), 120.3 (t), 113.9 (d), 100.1 (s), 69.8 (d), 66.8 (t), 64.0 (s), 63.4 (d), 33.9 (s), 29.7 (q), 20.1 (q), 18.7 (q); high-resolution mass spectrum m/z calcd for $C_{17}H_{24}NO_5S$ 354.1375, found 354.1370.

Benzyl 6-(α-*tert*-Butylvinylidene)penicillinate *S,S*-Dioxide (56d). To a solution of the sulfide **35d** (120 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) and pH = 6.4 buffer solution (5 mL) was added in one portion *m*-CPBA (85%, 132 mg, 0.65 mmol). The reaction mixture was stirred as rapidly as possible overnight at rt. After the layers were separated, the organic layer was washed (2×, 5% $NaHSO_3$, 5 mL), dried (Na_2SO_4), concentrated, and chromatographed (1:1 CH_2Cl_2/hexane) to yield a white solid **56d** (80 mg, 62% yield): R_f = in 1:1 CH_2Cl_2/hexane; IR ($CHCl_3$) 1960, 1780, 1740, 1315, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (5 H, br s), 6.09 (1 H, d, J = 1.5), 5.27 (2 H, ABq), 5.19 (1 H, d, J = 1.5), 4.44 (1 H, s), 1.55 (3 H, s), 1.31 (3 H, s), 1.15 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 197.5 (s), 168.0 (s), 167.0 (s), 136.1 (s), 128.8 (d), 113.9 (d), 100.1 (s), 69.7 (d), 68.1 (t), 64.1 (s), 63.3 (d), 33.9 (s), 29.7 (q), 20.0 (q), 18.7 (q).

Allyl 6-[(2′-Methoxyphenyl)vinylidene]penicillinate *S,S*-Dioxide (57b) (3:1 Ratio of Diastereomers). This compound was prepared from the sulfide **38b** as described in **56d** (yield = 22%): R_f = 0.86 in CH_2Cl_2; IR ($CHCl_3$) 1950, 1790, 1755, 1330, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (2 H, m), 7.33 and 7.28 (1 H, s), 6.97 (2 H, m), 5.98 (1 H, m), 5.39 (2 H, m), 5.27 and 5.24 (1 H, s), 4.75 (2 H, m), 4.48 and 4.41 (1 H, s), 3.90 and 3.87 (3 H, s), 1.65 and 1.63 (3 H, s), 1.47 and 1.44 (3 H, s).

6-Vinylidenepenicillanic Acid (46a). This compound was prepared as described for **44a** below to give **46a** as a white solid (50% yield): R_f = 0.26 in 1:3 CH_3OH/CH_2Cl_2; IR ($CDCl_3$ and CD_3OD) 3350, 1935, 1690, 1600 cm^{-1}; ^1H NMR ($CDCl_3$ and CD_3-

OD) δ 7.80 (1 H, br s), 5.76 (1 H, s), 5.36 (2 H, s), 4.35 (1 H, s), 1.55 (3 H, s), 1.45 (3 H, s); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 199.6, 169.9, 168.6, 107.8, 83.8, 70.1, 68.1, 64.7, 32.5, 26.0.

6-(α-Bromovinylidene)penicillanic Acid (28a). To a solution of the ester **28c** (470 mg, 1 mmol) in anisole (3 mL, 30 mmol) at 0 °C was added trifluoroacetic acid (9 mL, 117 mmol). After the solution was stirred for 10 min, the solvents were removed in high vacuum at rt. CH_2Cl_2 (25 mL) was added, and the solution was extracted with cold dilute $NaHCO_3$. The aqueous layer was acidified with cold dilute HCl into EtOAc. The organic layer was removed, washed (saturated NaCl), dried (Na_2SO_4), concentrated, and chromatographed (CH_2Cl_2, 1:49, 1:19, 1:9, 1:3 CH_3OH/CH_2Cl_2) to give a gummy solid (120 mg, 39% yield): R_f = 0.24 in 1:3 CH_3OH/CH_2Cl_2; IR ($CDCl_3$) 1950, 1770, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 6.59 (1 H, s), 5.89 (1 H, s), 4.37 (1 H, s), 3.35 (1 H, br), 1.56 (3 H, s), 1.49 (3 H, s); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 194.2, 171.7, 165.9, 119.9, 113.8, 71.7, 67.3, 65.1, 32.7, 25.8.

6-(α-*tert*-Butylvinylidene)penicillanic Acid (35a). To a solution of the allene **35b** (546 mg, 1.7 mmol) in THF (10 mL) was added in rapid succession triphenylphosphine (131 mg, 0.5 mmol), tetrakis(triphenylphosphine)palladium (98 mg, 0.085 mmol), and acetic acid (1.14 mL, 20 mmol). After the solution was stirred at room temperature for 1 h, the solvent was removed in vacuo and CH_2Cl_2 was added. The mixture was extracted with cold dilute $NaHCO_3$, and the aqueous layer was acidified with cold dilute HCl into EtOAc. The EtOAc layer was dried and concentrated to give pure **35a** as a white solid (100 mg, 21% yield): R_f = 0.32 in 1:3 CH_3OH/CH_2Cl_2; IR ($CDCl_3$) 1965, 1760, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.86 (1 H, s), 5.81 (1 H, s), 4.45 (1 H, s), 1.64 (3 H, s), 1.56 (3 H, s), 1.14 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 194.5 (s), 173.0 (s), 169.5 (s), 112.2 (d), 109.3 (s), 70.0 (d), 68.7 (d), 64.8 (s), 33.6 (s), 32.2 (q), 29.8 (q), 26.2 (q); high-resolution mass spectrum *m/z* calcd for $C_{14}H_{19}NO_3S$ 281.1085, found 281.1086.

6-(α-*tert*-Butylvinylidene)penicillanic Acid *S,S*-Dioxide (56a). This compound was prepared from **56b** as described for **35a** above to give after chromatography (CH_2Cl_2, 1:19, 1:9, 1:3 CH_3OH/CH_2Cl_2) **56a** as a white solid (36% yield): R_f = 0.40 in 1:3 CH_3OH/CH_2Cl_2; IR ($CDCl_3$) 3450, 1960, 1780, 1590, 1320, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.62 (1 H, br), 6.11 (1 H, d, *J* = 1.4), 5.23 (1 H, d, *J* = 1.4), 4.42 (1 H, s), 1.63 (3 H, s), 1.51 (3 H, s), 1.14 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 197.7 (s), 170.2 (s), 168.5 (s), 113.9 (d), 99.5 (s), 69.5 (d), 64.0 (s), 63.0 (d), 33.8 (s), 29.5 (q), 19.7 (q), 18.2 (q); high-resolution mass spectrum *m/z* calcd for $C_{14}H_{19}NO_5S$ 393.0983, found 393.0983.

6-[α-*tert*-Butyl-β-[(*p*-chlorophenyl)sulfenyl]vinylidene]penicillanic Acid (39a). This compound was prepared as described for **35a** above to give **39a** as a white solid (85% yield): R_f = 0.09 in CH_2Cl_2; IR ($CDCl_3$) 1950, 1775, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.37 (2 H, A of ABq, *J* = 8.5), 7.26 (2 H, B of ABq, *J* = 8.5), 6.55 (1 H, br), 5.59 (1 H, s), 4.13 (1 H, s), 1.39 (3 H, s), 1.26 (12 H, s); high-resolution mass spectrum *m/z* calcd for $C_{20}H_{22}{}^{35}ClNO_3S_2$ 423.0731, found 423.0723.

6-(α-Phenyl-β-methylvinylidene)penicillanic Acid (42a). This compound was prepared as described in **35a** above to give **42a** as a white solid (38% yield): R_f = 0.11 in CH_2Cl_2; IR ($CDCl_3$) 3200, 1955, 1785 cm^{-1}; 1710; ^{1}H NMR ($CDCl_3$) δ 8.55 (1 H, br), 7.40 (5 H, m), 5.92 (1 H, s), 4.59 (1 H, s), 2.27 (3 H, s), 1.71 (3 H, s), 1.60 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 198.3 (s), 173.0 (s), 169.4 (s), 133.6 (s), 128.7 (d), 126.6 (d), 110.9 (s), 108.9 (s), 70.2 (d), 68.9 (d), 65.0 (s), 32.2 (q), 26.2 (q), 16.8 (q); high-resolution mass spectrum *m/z* calcd for $C_{17}H_{17}NO_3S$ 315.0929, found 315.0925.

6-[α-Phenyl-β-(2′-oxopyrrolidylmethyl)vinylidene]penicillanic Acid (44a). To a solution of **44c** (400 mg, 0.71 mmol), in CH_2Cl_2 (4 mL), and anisole (4 mL) at −78 °C was added a solution of $AlCl_3$ (1.42 mL, 1 M in nitrobenzene) in one portion. The mixture was stirred for 10 min at −78 °C and poured into a separatory funnel containing CH_2Cl_2 (30 mL) and 1 N HCl (20 mL). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2×, 10 mL). The combined cloudy organic washings were extracted with pH = 7.4 buffer solution (2×, 50 mL). The combined extracts were acidified in the presence of EtOAc (20 mL) with 2 N HCl to pH = 4. The aqueous layers were washed with additional EtOAc (20 mL). The combined EtOAc layers were washed [saturated NaCl (2×, 5 mL)], dried (Na_2SO_4), concentrated, and chromatographed (CH_2Cl_2, 1:9, 1:3, and 1:1 CH_3OH/CH_2Cl_2) to give a white solid **44a** (158 mg, 55% yield): R_f = 0.54 in 1:3 CH_3OH/CH_2Cl_2; IR (Nujol mull) 1965, 1760, 1728, 1628 cm^{-1}; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.45 (5 H, br s), 5.94 (1 H, s), 4.45 (2 H, ABq), 4.41 (1 H, s), 3.56 (1 H, br s), 3.43 (2 H, m), 2.43 (2 H, m), 1.98 (2 H, m), 1.57 (3 H, s), 1.49 (3 H, s); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 195.7 (s), 175.7 (s), 174.8 (s), 168.4 (s), 131.2 (s), 128.8 (d), 127.7 (s), 126.6 (d), 111.7 (s), 111.2 (s), 72.6 (d), 68.2 (d), 65.6 (s), 47.2 (t), 42.6 (t), 32.5 (q), 30.7 (t), 26.1 (q), 17.4 (t).

Biological Assay. 50 mM pH 7.2 phosphate buffer was prepared by dissolving anhyd NaH_2PO_4 (0.840 g) and anhyd Na_2HPO_4 (2.56 g) in 500 mL of deionized (milipore) water. A solution of the β-lactamase derived from *E. cloacae* P99[22] in 50 mM pH 7.2 phosphate buffer (1.00 mg of enzyme was dissolved in 100 mL of buffer) was prepared. A standard solution of a lactamase substrate, cephalothin, was prepared by dissolving 20.0 mg of cephalothin in 10.0 mL of phosphate buffer. These two standard solutions were allowed to equilibrate to 25.0 °C in a water bath for at least 15 min.

To determine the rate of enzymatic hydrolysis of cephalothin in the absence of inhibitor, 514.6 μL of the standard cephalothin solution was further diluted with 385.4 μL of buffer and the new solution allowed to equilibrate to 25.0 °C in a water bath for 10 min. (This is the amount of cephalothin necessary to bring the concentration of this substrate to 2.46 mM[23] when the volume is eventually brought to 1.0 mL.) 100 μL of the enzyme solution was then added to the second cephalothin solution (bringing the total volume to 1.00 mL) and the ultraviolet absorption at 292 nm observed spectrophotometrically (without delay). The decay of this absorption was linear for approximately 4 min with a rate measured at 0.191 absorbance units per min over the first 2 min.

To evaluate inhibitors, a solution of inhibitor (1.0 mg of inhibitor in 10 mL buffer, 0.1 μg/μL in phosphate buffer) was prepared and equilibrated to 25 °C. A specific amount (in the case of **56a**, an aliquot of volume from 10 μL to 250 μL, which corresponds to 1 μg to 25 μg of **56a**) of the inhibitor solution was then added to 100 μL of the enzyme solution and the mixture allowed to incubate at 25.0 °C for 10 min. This partially inhibited enzyme was then added to a (equilibrated) solution prepared from the standard cephalothin solution (514.6 μL) and enough phosphate buffer to make the total volume 1.00 mL (total volume = volume of aliquat of inhibitor solution + 100 μL of enzyme solution + 514 μL of standard cephalothin solution + volume of phosphate buffer solution). Decay of the 292 absorption was immediately observed for 2.0 min and the % inhibition calculated by comparing the rate with the 0.191 rate observed for the hydrolysis with no inhibitor present.

For **56a**, the results showed 56.5% inhibition at the addition of 10 μL of the inhibitory solution (1.0 μg of inhibitor/1.0 μg of lactamase); 94.8% inhibition was observed on the addition of 50 μL of the inhibitor solution (5.0 μg of inhibitor/1.0 μg of lactamase); 99.5% inhibition was observed on the addition of 100 μL of the inhibitor solution (10.0 μg of inhibitor/1.0 μg of lactamase).

Acknowledgment. This research was supported by the National Institutes of Health, the Robert A. Welch Foundation, American Cyanamid, and the Petroleum Research Fund, administered by the American Chemical Society.

Supplementary Material Available: NMR spectra of **6a–d, 7b–d, 9b–d, 10b–d, 11b–14b, 15d, 16d, 17b,c, 18b,c, 19b–22b, 23c–26c, 27b–d, 28a–d, 29b–31b, 31c, 32b, 33b, 34c, 35a–d, 36b–d, 37d, 38b, 39a,b, 40d, 41b–43b, 41a, 44a,c, 45c–50c, 46a, 52b, 53b, 54c, 55b,d, 56a,b,d,** and **57b** (79 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(22) See ref 18.

(23) This is a convenient concentration at which to study the hydrolysis: Pratt, R. F. *Science* **1989**, *246*, 917.