7-Alkylidenecephalosporin Esters as Inhibitors of Human Leukocyte Elastase

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A series of 7-alkylidenecephalosporins and 7-vinylidenecephalosporins, as their benzhydryl esters, have been tested as inhibitors of both porcine pancreatic elastase and human leukocyte elastase. Selected 7-alkylidenecephalosporin esters are found to be potent inhibitors of HLE. One category of new inhibitors is the 7-(haloalkylidene)cephalosporins. In contrast to previously reported cephalosporin-based elastase inhibitors, these haloalkylidene cephems show optimum inhibitory activity as sulfides, rather than as sulfones. They are efficient and irreversible inhibitors. A second class of active compounds is represented by the benzhydryl ester 7-(cyanomethylidene)cephalosporin sulfone. In contrast to the activity of these new inhibitors, the benzhydryl ester of the mechanism-based β-lactamase inhibitor, 7-[(2′-pyridyl)methylidene]-cephalosporin sulfone showed little inhibitory activity as an elastase inhibitor. 7-Vinylidenecephalosporins were also relatively poor inhibitors, although the terminally unsubstituted allene sulfide showed activity as an inhibitor of PPE. A modeling analysis suggests the 7-alkylidene substituents can be readily accommodated in the S1 pocket. A potential mechanism of inhibition is proposed.

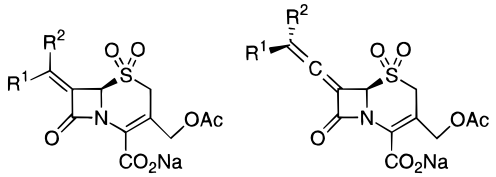
Introduction

Human leukocyte elastase (HLE) is a potent serine proteinase which has been implicated in the chronic tissue destruction mechanisms of several disease states including emphysema, acute respiratory distress syndrome (ARDS), atherosclerosis, and rheumatoid arthritis. HLE is stored in the azurophilic granules of polymorphonuclear leukocytes (PMN's) and is released in response to inflammatory stimuli. Under normal circumstances, it is believed that an appropriate balance exists between released HLE and endogenous inhibitors, which scavenge the enzyme. However, in certain disease states an imbalance occurs. This is usually due to the liberation of excessive HLE or to the impairment of the regulatory processes. Since HLE is capable of degrading a variety of structural proteins (including elastin, other components of connective tissue, and certain complement proteins and receptors), widespread tissue destruction ensues. In cigarette smokers, this imbalance can occur because of the oxidative inactivation of α-1-proteinase, an endogenous HLE inhibitor, by the smoke. Free HLE has been detected in the lung fluid of patients with chronic bronchitis and cystic fibrosis. A proposed treatment of such diseases involves the administration of low molecular weight HLE inhibitors.

The inhibition of HLE has been reviewed.[1] Recently it has been demonstrated that derivatized cephalosporins,[2] penicillins,[3] penems,[4] monocyclic β-lactams,[5] and nonconventional bicyclic β-lactams[6] can function as inhibitors of HLE. In the case of the cephalosporins, the mechanism of this inhibition has been explored by crystallographic,[7] kinetic,[8] and chemical[9] methods.

We have reported the β-lactamase inhibitory activity of a series of penicillins and cephalosporins having 6- and 7-position unsaturation, respectively.[10] Type A and C β-lactamases are serine hydrolases known to be extremely important in bacterial resistance to β-lactam antibiotic therapy. We have reported two new types of

Chart 1



β-lactamase inhibitors: the 7-alkylidenecephalosporins and 7-vinylidenecephalosporins, shown in Chart 1 in the sulfone oxidation state. Selected examples of such compounds can be potent inhibitors, especially of the class C β-lactamases, which prefer cephalosporins as substrates.

With the knowledge that cephalosporin esters, amides, and ketonic derivatives are potent HLE inhibitors, we decided to explore the possibility that some of the esterified intermediates *en route* to our previously reported β-lactamase inhibitors might possess the ability to inhibit elastase. The synthesis of these materials follows routes we had previously reported[10] and is summarized in Schemes 1 and 2. For comparison purposes, we also prepared the benzhydryl esters of a few of the (cephalosporin-derived) compounds previously reported by the Merck researchers[2] as shown in Scheme 3.

In Table 1 the results of this study are shown. In Figure 1 (parts A and B), the time dependence of a few of the best inhibitors is displayed at inhibitor to enzyme ratios of 20:1 and 5:1, respectively.

Results and Discussion

Several of the new compounds above display potent (HLE) inhibitory properties. These are of structural type **I** and fall into two classes: the 7-(haloalkylidene)-cephalosporins, such as **13** and **15**, which display optimum HLE inhibitory activity as sulfides, and the (cyanoalkylidene)cephalosporin, **31**, which displays HLE inhibitory activity in the sulfone oxidation state. In Figure 1A, the time dependence of this inhibition is examined. It can be seen that, in addition to the

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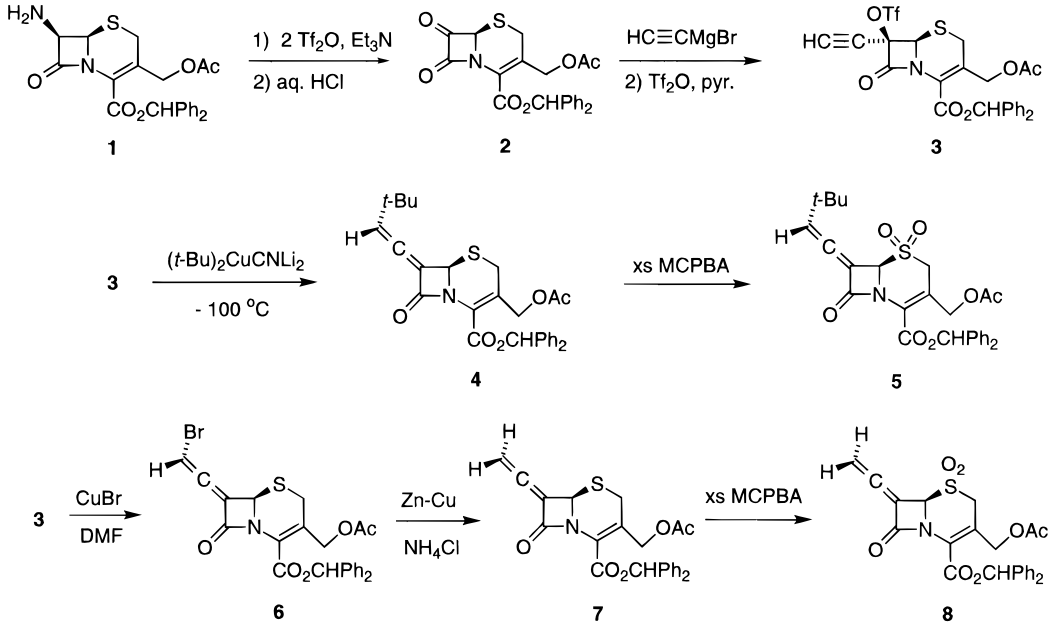
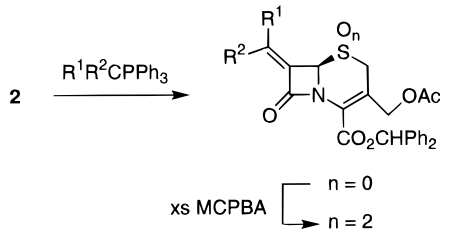
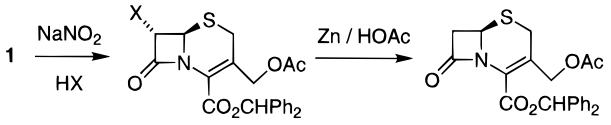
Scheme 1. General Synthesis of the 7-Vinylidenecephalosporins (**I**) and Corresponding Sulfones



Scheme 2. General Synthesis of the 7-Alkylidenecephalosporins (**II**) and Corresponding Sulfones



Scheme 3. General Synthesis of 7-Monosubstituted and Unsubstituted Cephalosporins (**III**)



7-dibromomethylidene sulfide **13** and the 7-monobromomethylidene sulfide **15**, the 7-dichloromethylidene sulfide **22** also possesses significant inhibitory activity (especially visible at longer incubation times). The pyridylmethylidene analog **21** (the benzhydryl ester of a potent β-lactamase inhibitor) showed no activity. Of the allenes prepared (structural type **II**), only the unsubstituted allene, **7**, showed moderate activity as an inhibitor of PPE.

In Figure 1B the time course of the inhibition of compounds **13**, **31**, and **32** is followed at an I:E ratio of 5:1 for 24 h. It can be seen that the haloalkylidene cephems are efficient and irreversible inhibitors. The cyanomethylidene cephem sulfone, **31**, however is not quite as efficient (requiring more than 5 equiv of inhibitor per equivalent of enzyme) or as irreversible as the halides.

In the absence of crystallographic information on the ability of the elastase active site to accommodate these 7-(alkylidene)cephalosporins (or any α-alkylidene β-lactam), we performed modeling studies on several of the compounds listed in Table 1 using the 1.84 Å resolution crystal structure of the human neutrophil elastase reported by Navia et al.[11] We began by investigating

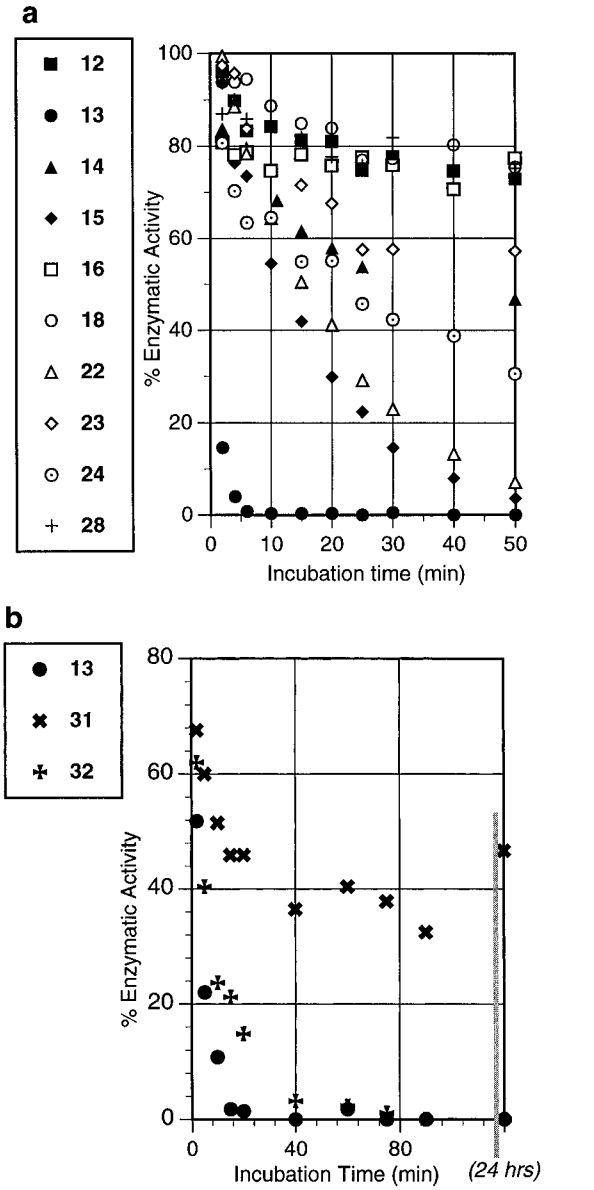
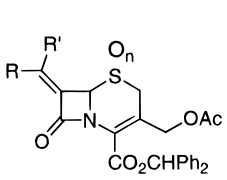
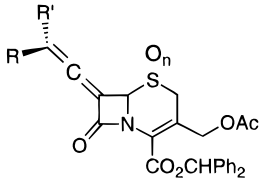


Figure 1. Plot of HLE hydrolytic activity upon incubation with selected 7-alkylidene cephalosporins at [I]/[E] = 20 (A) or [I]/[E] = 5 (B).

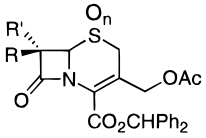
Table 1. Inhibition of PPE and HLE by 7-Vinylidene- and 7-Alkylidenecephalosporin Esters



I



II



III

compd	structure type	R	R′	n	IC$_{50}$ (mM) PPE	IC$_{50}$ (mM) HLE
1	III	NH_2	H	0	>10	>10
2	III	O	O	0	>10	>10
4	II	H	*t*-Bu	0	5.5	>10
5a	II	H	*t*-Bu	2	>10	10.5
5b	II	D	*t*-Bu	2	NT	13.5
6	II	H	Br	0	>10	5.4
7	II	H	H	0	0.67	9.0
8	II	H	H	2	4.1	6.1
9	I	H	Ph	0	>10	>10
10	I	H	Ph	2	>10	8.9
11	I	Ph	H	0	>10	>10
12	I	Ph	H	2	>10	6.0
13	I	Br	Br	0	6.42	0.26
14	I	Br	Br	2	4.8	2.07
15	I	Br	H	0	9.6	0.39
16	I	Br	H	2	2.49	3.36
17	I	H	$CO_2C(CH_3)_3$	0	NT	>10
18	I	H	$CO_2C(CH_3)_3$	2	>10	7.1
19	I	H	CHO	0	5.2	13.9
20	I	H	2′-Py	0	>10	>10
21	I	H	2′-Py	2	>10	>10
22	I	Cl	Cl	0	>10	6.41
23	I	Cl	Cl	2	>10	2.56
24	I	H	CO_2Me	0	>10	2.6
25	I	H	CO_2Me	2	>10	8.9
26	I	H	CH_2OH	0	>10	>10
27	I	H	CON(OMe)(Me)	2	>10	>10
28	I	H	$COCH_3$	0	>10	4.27
29	I	H	$COCH_3$	2	6.00	>10
30	I	H	CN	0	NT	>10
31	I	H	CN	2	NT	0.49
32	I	Br	CO_2Me	0	NT	0.21
33	III	H	H	0	>10	>10
34	III	H	I	0	5.6	1.18
35	III	H	Cl	0	2.9	6.0
36	III	H	OMe	0	NT	5.35
37	III	H	OMe	2	NT	0.28
38	III	Br	Br	0	NT	1.39
39	*N*-(methoxysuccinyl)-L-Ala-L-Ala-L-Pro-L-Val chloromethyl ketone					0.50

the conformational energetics of **13** as a function of the eight single bond rotations present using the Tripos 5.2 force field.[12] Additional conformations corresponding to rotation about the acetyl methyl group were not considered explicitly. Using the genetic algorithm incorporated in the Spartan package,[13] 45 conformations within 5 kcal mol^{-1} of the lowest energy structure were identified. Forty could be eliminated by inspection since they involved orientations of one or both phenyl groups that were stacked over the cephem moiety and were clearly incompatible with the confines of the elastase binding cavity. The remaining five were positioned into the elastase binding cavity in a manner analogous to that proposed by Doherty and co-workers.[2b] At this stage two more were eliminated on the basis of severe steric conflicts with the active site residues. The geometries of the remaining three, together with those of nearby active site residues, were energy minimized as described in the Experimental Section.

Figure 2A shows **13** docked into the elastase active site in the conformation predicted to lead to most favorable binding energy. As can be seen, the 7-alkylidene side chain is accommodated snugly within the S1 specificity pocket, which is roughly bounded by the resides Val190-Cys191-Phe192-Gly-193 on the "left" and Ser214-Phe215-Val216 on the "right" of the inhibitor. Elastase has a specificity for substrates with a small hydrophobic residues in the P1 position. Indeed, the Merck researchers observed that small, 7-position α-face side chains (such as the methoxy of cephalosporin sulfone **37**) produced excellent inhibitors.[2b] By contrast, cephalosporin antibiotics (which target the penicillin binding proteins) typically have relatively large β-oriented polar acylamido groups at the corresponding sp^3-hybridized 7-position.

Figure 2B compares the relative positions of **13** and **37** docked into the elastase active site (benzhydryl esters have been omitted in the figure only). There is a close superposition between the skeletal atoms of the two compounds for all but the 7-carbon. In the Merck compound (**37**), this is displaced "upwards" by ∼0.6 Å in order to preserve the locations of the 7-methoxy group and the carbonyl oxygen of the β-lactam ring imposed by the steric restraints of the S1 site and oxyanion hole

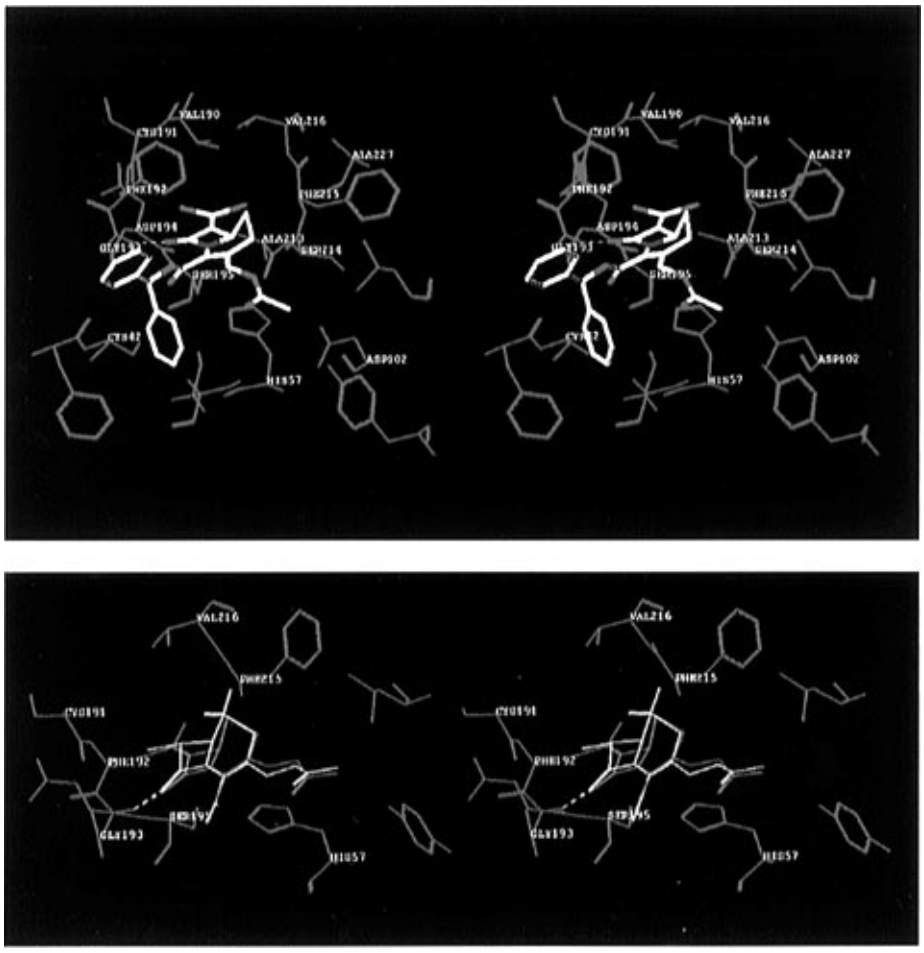


Figure 2. (a, Top) Stereoview of a modeled docking of **13** in the active site of HLE. With the exception of the N-H of GLY 193, all hydrogens have been omitted. (b, Bottom) Stereoview of a superposition of a modeled docking of **13** (orange) and **37** (yellow) in the active site of HLE. As above, all hydrogens, with the exception of the N-H of GLY 193 have been omitted. For clarity, the benzhydryl groups of both inhibitors and the phenyl group of PHE 192 have been omitted.

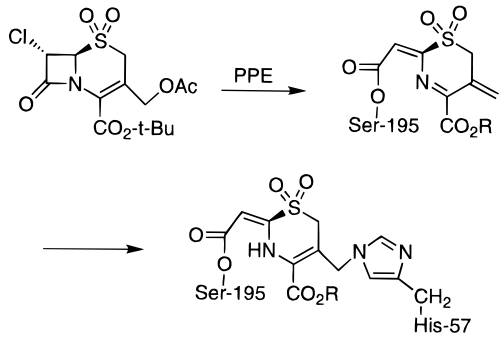
respectively. This has a small effect on the distance between the nucleophilic oxygen of Ser 195 and the carbon of the β-lactam carbonyl group which is ~5% greater in **37** than in **13**.

As mentioned above, the mechanism of inhibition of elastase by cephalosporins and other β-lactams is still an active area of investigation. Three important features of cephalosporin-derived elastase inhibitors include the 7-position substituent, the oxidation state of the sulfur at the 1-position, and the necessity for a 3′-position leaving group (such as acetoxy).

On the basis of an early X-ray crystallographic studies[7] of the reaction of one cephalosporin (3-(acetoxymethyl)-7-α-chloro-3-cephem-4-carboxylate 1,1-dioxide *tert*-butyl ester) with porcine pancreatic elastase (PPE), it is believed that the inhibitory activity of the cephalosporins is the result of a "hit" of the nucleophilic histidine-57 at the 3′-position of the cephalosporin as shown in Scheme 4.

Despite the reported similarity of the active sites of PPE and HLE,[11] we observed little or no correlation between inhibition of the two enzymes in the present study. It should also be noted that a 7-position halide (or other leaving group) is not a prerequisite for potent biological activity, and therefore, this crystallographically examined chloride is not necessarily representative of all cephalosporin-derived elastase inhibitors. For example, the initial Merck studies with substituted cephalosporins (all of which possess an sp^3-hybridized 7-position) established that a small, hydrophobic group

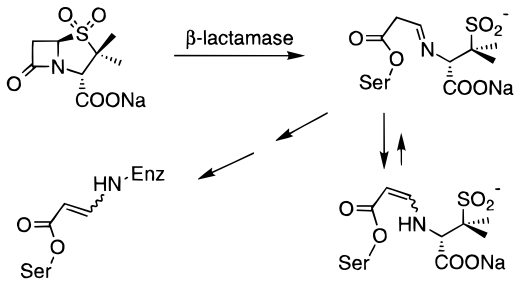
Scheme 4



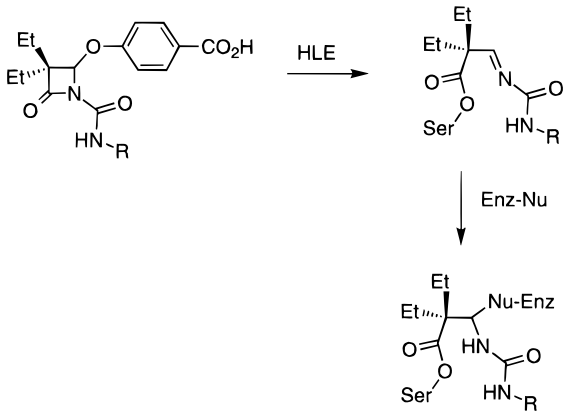
(for example methoxy, as in the case of compound **37**, or even a simple alkyl, such as ethyl) on the α-face of the cephem provided compounds with optimum (HLE) inhibitory activity.[2b]

A second important structural feature of previously described cephalosporin-based elastase inhibitors is the 1-position sulfone. Merck researchers noted that the cephalosporin esters were uniformly more biologically active as sulfones rather than as sulfides or sulfoxides.[2b] The electronegative sulfone group is believed to increase the reactivity of the β-lactam carbonyl. Following β-lactam enzymolysis, the sulfone can also function as a leaving group. This is mechanistically illustrated by the case of the (serine) β-lactamase inhibitor sulbactam. Knowles[14] and recently Mobashery[15] have provided evidence that the β-lactamase inhibition results from

Scheme 5



Scheme 6



the sulfone's serving as a leaving group after acyclation of the active site serine (as shown in Scheme 5). This elimination results in either the formation of a reactive imine (which can irreversibly trap a nucleophilic amino acid residue in the active site) or the tautomerization to a β-aminoacrylate (or "vinylogous urethane", which represents a hydrolytically stabilized acyl enzyme). A recent crystallographic study provides additional evidence for the presence of a β-aminoacrylate as a stable acylenzyme in the inhibition of a class C β-lactamase.[16]

Mechanistically related monocyclic elastase inhibitors were developed with two small substituents (usually ethyl or methyl groups) α to the β-lactam carbonyl (at position 3 of the 2-azetidinone) and a leaving group at position 4.[5a] Such compounds are believed to function by a double-hit mechanism, similar to that proposed for sulbactam (only with a histidine as the proposed second nucleophile) as shown in Scheme 6.[17] The *gem*-dialkyl substituents improve the hydrolytic stability of these compounds in blood, while only slightly reducing the inhibitory potency.[17]

A plausible mechanism of inhibition of the present inhibitors is shown in Scheme 7. Regarding the initial double bond isomerization, O'Connor and Lyness[18] have shown that such a prototropic rearrangement isomerization of allyl sulfides is highly favorable relative to that of allylic sulfones, potentially explaining the enhanced inhibitory activity of the (halogen-containing) sulfides relative to the sulfones. Our modeling study indicates that His-57 is located in reasonable proximity to the hydrogen at C-6 to function as the basic catalyst.

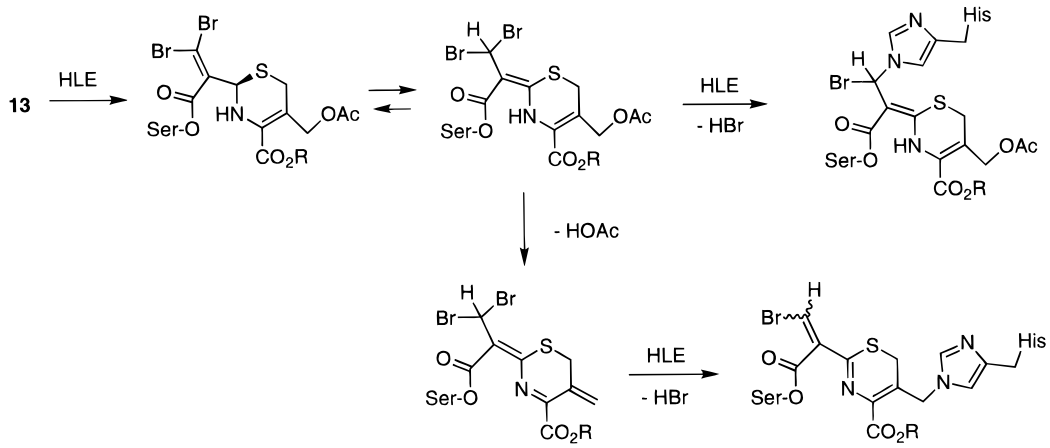
Conclusion

We have synthesized a series of benzhydryl 7-alkylidenecephalosporinates and benzhydryl 7-vinylidenecephalosporinates, both as sulfides and as sulfones, and evaluated them as inhibitors of HLE and PPE. We have found that 7-(haloalkylidene)cephalosporinate sulfides **13**, **15**, **22**, and **32** and 7-(cyanoalkylidene)cephalosporinate sulfone **31** are potent, irreversible inhibitors of HLE. A modeling study of inhibitor **13** illustrates that 7-methylidenecephalosporins readily dock in the active site of HLE with the alkylidene substituent in the S1 pocket. A plausible mechanism of inhibition is proposed which, subsequent to formation of the acyl enzyme, involves an isomerization of the alkylidene double bond.

Experimental Section

All assays of elastase activity were performed on a Beckman DU-650 spectrophotometer, and hydrolysis rates of the elastase substrate, *N*-(methoxysuccinyl)-L-alanyl-L-alanyl-L-prolyl-L-valine 4-nitroanilide, were monitored at 410 nm. This substrate was purchased from Fluka Chemical Corp. (Ronkonkoma, NY). Melting points are uncorrected and determined on a Mel-Temp capillary melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 710B diffraction grating spectrophotometer or a Perkin-Elmer 1600 Series Fourier transform infrared spectrophotometer. ^{1}H 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 chloroform-*d* (77.0) as the reference. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Mass spectral data were obtained by FAB techniques from the Midwest Center for Mass Spectrometry at the University of Nebraska−Lincoln, Lincoln, NE. Thin layer chromatography (TLC) was performed on Merck 0.2 mm Kieselgel 60 F_{254} silica-coated aluminum plates. The compounds were identified in one or more of the following manners: UV (254 nm), iodine chamber, and/or phosphomolybdic acid spray reagent. The position of the compounds on the TLC plate are listed as an R_f value in the

Scheme 7. Proposed Mechanism for the Inhibition of HLE by **13**



given solvent(s). Flash chromatography was performed by using thick-walled glass columns and Merck's 0.040−0.063 mm Kieselgel 60 silica gel. The (flash) chromatography solvents were distilled from calcium hydride before use. All additional solvents were obtained from Aldrich in Sure-Seal bottles.

Both HLE and PPE was purchased from Elastin Products Company, Inc. (Owensville, MO). Trizma Base and Trizma Hydrochloride were both obtained from Sigma Chemical Co. (St. Louis, MO). All other reagents were used as received from Aldrich unless otherwise noted. Unless otherwise specified, all yields refer to the isolation of purified material (after chromatography).

IC_{50} Determination. The 0.1 M Tris-NaCl buffer solution of pH 7.5 was prepared by dissolving 12.7 g of Tris-HCl, 2.36 g of Tris-base, 29.22 g of NaCl, and 0.1 g of NaN_3 in 900 mL of H_2O. The pH was determined and was brought to 7.5 at 25 °C with 0.1 M HCl or 0.1 M NaOH, if necessary. The volume was increased to 1 L with water. The NaOAc−NaCl buffer was prepared by combining 0.2 M HOAc (14.8 mL), 0.2 M NaOAc (35.2 mL), and 100 mL of 0.2 M NaCl. Then, 0.1 g of NaN_3 was added, and the volume was brought to 200 mL with water. The human leukocyte elastase solution was prepared by adding HLE (0.36 mg) to 1 mL of NaCl−NaOAc buffer. The inhibitor solutions were prepared by dissolving 1 mg of the specified inhibitor in 1 mL of DMSO. With exceptionally good inhibitors, dilutions of this solution were made by taking 10 μL of the inhibitor solution and increasing the volume to 100 μL with DMSO.

For the determination of the IC_{50}, a specified volume (0−20 μL) of the inhibitor solution was diluted with 20 μL of Tris buffer and enough DMSO to bring the total volume to 40 μL. Then 10 μL of the elastase solution was added and the mixture allowed to incubate for 4 min. A 40 μL sample of this solution was then withdrawn and added to a solution of 50 μL of substrate solution in 900 μL of Tris buffer. The hydrolysis rate of the substrate was determined spectrophotometrically by monitoring the absorbance at 410 nm for 2 min at 1 s intervals.

For the time-dependence studies of Figure 1, enzyme solution (1 mL, 2.44 μM) was incubated with inhibitor at the appropriate molar ratio of inhibitor to enzyme (either 20:1 or 5:1). Aliquats (40 μL) were then removed at appropriate time intervals (initially every 2 min, then gradually increasing to every hour as the inhibition progressed). These aliquats were immediately diluted into a solution of substrate in buffer (as described above) to measure the remaining activity of the enzyme. A control was performed, in the absence of inhibitor, to ensure that the enzyme maintained its activity in solution.

Computational Methods. The atomic coordinates of elastase used in the modeling studies were taken from the reported[11] geometry of human neutrophil elastase complexed with the synthetic inhibitor methoxy succinyl-Ala-Ala-Pro-Ala chloromethyl ketone (Protein Data Bank file: 1HNE). After the inhibitor and crystallographic water molecules were deleted, the essential hydrogen atoms were added using Tripos Associates molecular modeling software, Sybyl.[19] Partial energy minimization of cephem derivatives docked in the elastase active site were carried out using the annealing functions of Sybyl. In all cases the Tripos 5.2 force field was used with Gasteiger/Hückel charges for both the enzyme and inhibitor. The latter, together with all residues with atoms falling within 6 Å of any of the inhibitor atoms, were subject to complete energy minimization. The nonbonded potential of those atoms falling within 6−12 Å of the inhibitor were also included in the energy calculation, although their relative positions remained fixed. Electrostatic interactions were computed using a distance dependent dielectric function. A nonbonded cutoff of 8 Å was used.

Synthesis. Compounds **33**−**38** were synthesized for comparison purposes only as described by Doherty.[2b]

Benzhydryl 7β-Aminocephalosporanate (1). To a suspension of 7-aminocephalosporanic acid (130.4 g, 0.48 mol) in methanol (480 mL) was added a solution of diphenyldiazomethane (93.0 g, 0.48 mol) in CH_2Cl_2. The reaction was then mechanically stirred at room temperature for 44 h. The remaining solid was removed by filtration. The resultant filtrate was concentrated *in vacuo* and purified by column chromatography (10% CH_3OH in CH_2Cl_2) to afford the desired ester as pale yellow solid (86.1 g, 41% yield): R_f = 0.44 in 1:9 CH_3OH:CH_2Cl_2; mp 45−46 °C; IR ($CHCl_3$) 2980, 1780, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41 (2H, bs), 7.22 (10H, m), 6.91 (1H, s), 5.27 (1H, d, J = 2.8 Hz), 5.15 (1H, d, A of AB q, J = 14 Hz), 4.94 (1H, s), 4.84 (1H, d, B of AB q, J = 14 Hz), 3.73 (1H, d, A of AB q, J = 17 Hz), 3.33 (1H, d, B of AB q, J = 17 Hz), 1.92 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.8, 168.8, 160.6, 138.9, 138.7, 129.5, 129.3, 129.1, 128.7, 128.5, 127.97, 127.61, 127.52, 127.18, 126.52, 126.06, 125.4, 79.0, 63.3, 62.6, 58.5, 25.7, 20.1.

Benzhydryl 7-Oxocephalosporanate (2). The title compound was prepared by modifying the procedure of Hagiwara.[20] To a solution of benzhydryl 7β-aminocephalosporanate (5.9 g, 13.5 mmol) in anhydrous CH_2Cl_2 (70 mL) at −78 °C was added dropwise triethylamine (5.6 mL, 40.4 mmol) with stirring. After 5 min, trifluoromethanesulfonic anhydride (6.8 mL, 40.4 mmol) was added dropwise to this solution over a 5 min period. The reaction mixture was allowed to warm slowly to 0 °C over a 1 h period. It was then recooled to −78 °C, and triethylamine (5.6 mL, 40.4 mmol) was added over approximately 10 min. The reaction mixture was stirred at −78 °C for an additional 30 min and poured into 200 mL of cold 0.5 N HCl. The resultant mixture was further stirred until the ice melted. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (150 mL). The combined organic layers were washed with cold 0.5 N HCl (3 × 100 mL), dried (Na_2SO_4), and concentrated (at room temperature or below) to produce the title compound (5.8 g, 98% yield) as a brown solid which was used without further purification: IR ($CHCl_3$) 3005, 1830, 1790, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (10H, m), 7.05 (1H, s), 5.32 (1H, s), 5.07 (1H, d, A of AB q, J = 14 Hz), 4.85 (1H, d, B of AB q, J = 14 Hz), 3.64 (1H, d, A of AB q, J = 18 Hz), 3.44 (1H, d, B of AB q, J = 18 Hz), 2.05 (3H, s); ^{13}C NMR ($CDCl_3$) δ 188.4 (s), 170.3 (s), 160.1 (s), 158.7 (s), 138.8 (s), 138.6 (s), 128.4, 128.2, 128.1, 127.7, 126.9, 126.2, 80.1 (d), 65.8 (d), 62.6 (t), 27.7 (t), 20.4 (q).

Benzhydryl 6α-ethynyl-6β-hydroxycephalosporanate. Ethynylmagnesium bromide (45.2 mL, 22.6 mmol) was slowly added to the cold (−78 °C) solution of 7-oxocephalosporanate (**2**) (5.5 g, 12.6) in anhydrous THF (85 mL). It was then further stirred at −78 °C for 1 h and at −40 °C for 90 min. The reaction mixture was then quenched with acetic acid (2.9 mL, 50.4 mmol), and the product was extracted with ether (2×, 100 mL). The combined organic layers were washed with water (1×, 30 mL) and brine (1×, 30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. It was then purified by column chromatography (1:4 EtOAc:CH_2Cl_2) to give the title compound (2.9 g, 50% yield) as a pale yellowish solid: R_f = 0.56 in 1:4 EtOAc:CH_2Cl_2; mp 50−52 °C; IR ($CHCl_3$) 3670, 3565, 3300, 3010, 2120, 1790, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (10H, m), 6.95 (1H, s), 5.14 (1H, d, A of AB q, J = 13.9 Hz), 5.08 (1H, s), 4.89 (1H, d, B of AB q, J = 13.9 Hz), 3.53 (1H, d, A of AB q, J = 17.8 Hz), 3.35 (1H, d, B of AB q, J = 17.8 Hz), 2.88 (1H, s), 2.05 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.7 (s), 162.7 (s), 160.3 (s), 139.3 (s), 139.1 (s), 132.1 (s), 128.42, 128.0, 127.3, 126.9, 125.6, 79.6 (d), 78.3 (s), 77.9 (s), 77.3 (d), 65.4 (d), 62.6 (t), 26.3 (t), 20.5 (q). Anal. ($C_{25}H_{21}NO_6S$) C, H, N.

Two more compounds were isolated from this reaction: **1. Benzhydryl 6β-ethynyl-6α-hydroxycephalosporinate:** yellow solid (0.58 g, 10% yield); R_f = 0.041 in 1:4 EtOAc:CH_2Cl_2; IR ($CHCl_3$) 3550, 3300, 3010, 2105, 1780, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (10H, m), 6.92 (1H, s), 6.45 (1H, d, J = 1.3 Hz), 5.30 (1H, s), 5.19 (1H, d, J = 1.3 Hz), 4.63 (2H, s), 2.80 (1H, s), 2.05 (OH, s), 1.99 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.7 (s), 165.6 (s), 162.8 (s), 138.8 (s), 128.5, 128.2, 127.6, 127.4, 126.8, 126.6, 122.1 (d), 119.2 (s), 78.9 (s), 78.8 (d), 77.6 (d), 76.9 (s), 65.5 (t), 61.0 (d), 50.2 (d), 20.4 (q). **2. Benzhydryl 6β-hydroxycephalosporanate:** pale yellow solid (0.59 g, 10% yield); R_f = 0.26 in 1:4 EtOAc:CH_2Cl_2; IR ($CHCl_3$) 3680, 3350, 3010, 1795, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (10H, m), 6.93 (1H, s), 5.39 (1H, d, J = 4.9 Hz), 5.15 (1H, d, A of AB q, J = 13.8 Hz), 4.97 (1H, d, J = 4.8 Hz), 4.81 (1H, d, B of AB q, J = 13.8 Hz), 3.57 (1H, d, A of AB q, J = 18.6 Hz), 3.39 (1H, d, B of AB q, J = 18.7 Hz), 2.16 (OH, s), 2.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.7 (s), 162.5 (s), 160.3 (s), 139.0 (s), 138.7 (s), 129.4, 128.5, 128.4, 128.3, 128.1, 127.7, 127.0, 80.0 (d), 62.4 (d), 57.2 (d), 26.3 (t), 20.4 (q).

Benzhydryl 6α-ethynyl-6β-(trifluoromethanesulfonato)-cephalosporanate (3). Trifluoromethanesulfonic anhydride (3.3 mL, 19.1 mmol) was added dropwise (4 s intervals) to a cold (0 °C) solution of pyridine (2.6 mL, 31.8 mmol) and benzhydryl 6α-ethynyl-6β-hydroxycephalosporanate (5.9 g, 12.7 mmol) in anhydrous CH_2Cl_2 (60 mL). The reaction mixture was allowed to warm to room temperature and monitored by TLC (reaction time = 30 min). After concentration the residue was purified by column chromatography (CH_2Cl_2) to yield the title compound as a white solid (4.67 g, 62% yield): R_f = 0.63 in 15% EtOAc in CH_2Cl_2; mp 42−43 °C; IR ($CHCl_3$) 3300, 3020, 2120, 1810, 1780, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (10H, m), 6.94 (1H, s), 5.29 (1H, d, A of AB q, J = 13.9 Hz), 5.26 (1H, s), 5.09 (1H, d, B of AB q, J = 14.8 Hz), 3.52 (1H, d, A of AB q, J = 16.5 Hz), 3.34 (1H, d, B of AB q, J = 18.3 Hz), 3.29 (1H, s), 2.09 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 159.4 (s), 155.1 (s), 140.8 (s), 139.2 (s), 139.1 (s), 128.5, 128.1, 126.9, 126.8, 125.3, 118.0 (q, J = 321.11 Hz), 87.3 (s), 84.0 (d), 79.6 (d), 71.9 (s), 66.5 (d), 61.7 (t), 26.5 (t), 20.4 (q). Anal. ($C_{26}H_{20}F_3NO_8S_2$) C, H, N.

Benzhydryl 7α-(*tert*-butylvinylidene)cephalosporanate (4). To a suspension of CuCN (0.376 g, 4.2 mmol) in anhydrous THF (30 mL) was added *t*-BuLi (4.0 mL, 6.8 mmol) at −100 °C. The cooling bath was removed until all the solid had gone into the solution (approximately 3 min). This solution was again cooled to −100 °C and was cannulated into a cold solution of benzhydryl 6α-ethynyl-6β-(trifluoromethanesulfonato)cephalosporanate (**3**) (2.0 g, 3.4 mmol) in anhydrous THF (5 mL) at −100 °C. The solution was further stirred at −100 °C for 1 min before quenching with saturated NH_4Cl solution. The reaction mixture was extracted with ether (2×, 50 mL), dried (Na_2SO_4), concentrated, and chromatographed (5% EtOAc in CH_2Cl_2) to give a white fluffy solid (0.913 g, 54% yield): R_f = 0.80 in 5% EtOAc in CH_2Cl_2; mp 113−114 °C; IR ($CHCl_3$) 3000, 2960, 1970, 1770, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (10H, m), 7.05 (1H, s), 5.98 (1H, d, J = 1.63 Hz), 5.25 (1H, d, J = 1.69 Hz), 4.97 (1H, d, A of AB q, J = 13.30 Hz), 4.72 (1H, d, B of AB q, J = 13.23 Hz), 3.55 (1H, d, A of AB q, J = 18.14 Hz), 3.35 (1H, d, B of AB q, J = 18.23 Hz), 2.01 (3H, s), 1.18 (9H, s); ^{13}C NMR ($CDCl_3$) δ 194.6 (s), 170.2 (s), 161.1 (s), 159.5 (s), 139.2 (s), 139.0 (s), 128.3, 128.0, 127.9, 127.7, 127.1, 121.9, 113.2 (d), 107.2 (s), 79.6 (d), 63.0 (t), 57.0 (d), 33.6 (s), 29.7 (q), 27.8 (t), 20.5 (q). Anal. ($C_{29}H_{29}NO_5S$) C, H, N.

Benzhydryl 7α-(*tert*-butylvinylidene)cephalosporanate sulfone (5). General Procedure for the Preparation of Cephalosporin Sulfones: To a solution of sulfide **4** (0.252 g, 0.5 mmol) in CH_2Cl_2 (10 mL) and pH = 6.4 buffer solution (10 mL) was added *m*-CPBA (85%, 0.35 g, 2.0 mmol) in one portion. The mixture was stirred at room temperature, for 40 min, and then ether (50 mL) was added. After the layers were separated, the organic layers were washed with saturated $NaHCO_3$ (3 × 30 mL), dried ($NaSO_4$), concentrated, and purified by column chromatography to yield a white solid (yield = 65%, 0.174 g): R_f = 0.42 in 2% EtOAc in CH_2Cl_2; mp 163−164 °C; IR ($CHCl_3$) 3010, 2960, 1970, 1790, 1740, 1340, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (10H, m), 7.01 (1H, s), 6.18 (1H, d, J = 1.66 Hz), 5.30 (1H, s), 5.02 (1H, d, A of AB q, J = 13.93 Hz), 4.68 (1H, d, B of AB q, J = 13.93 Hz), 4.02 (1H, d, A of AB q, J = 18.27 Hz), 3.76 (1H, d, B of AB q, J = 18.20 Hz), 2.03 (3H, s), 1.19 (9H, s); ^{13}C NMR ($CDCl_3$) δ 197.1 (s), 170.1 (s), 160.0 (s), 158.6 (s), 138.8 (s), 138.7 (s), 128.5, 128.3, 128.2, 127.6, 127.1, 126.5, 123.1, 114.6 (d), 100.1 (s), 80.4 (d), 70.1 (d), 62.0 (t), 51.2 (t), 34.0 (s), 29.7 (q), 20.4 (q). Anal. ($C_{29}H_{29}NO_7S$) C, H, N.

Benzhydryl 7-(α-Bromovinylidene)cephalosporanate (6). Method A. Copper(I) bromide (CuBr, 133 mg, 0.93 mmol) was added in one portion to a solution of benzhydryl 6α-ethynyl-6β-(trifluoromethanesulfonato)cephalosporanate (500 mg, 0.84 mmol) in anhydrous DMF (5.0 mL) at room temperature and stirred in the dark for 30 min. The DMF was removed *in vacuo* at room temperature. The residue was dissolved in ether (50 mL), washed with water (2x, 15 mL), dried (Na_2SO_4), and concentrated to give yellow solid. This material was purified by column chromatography (CH_2Cl_2) to yield title compound as pale yellow solid (140 mg, 32% yield): R_f = 0.75 in 15% EtOAc in CH_2Cl_2; mp 63−65 °C; IR ($CHCl_3$) 3010, 1950, 1780, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (10H, m), 7.01 (1H, s), 6.74 (1H, d, J = 1.17 Hz), 5.38 (1H, d, J = 1.12 Hz), 5.02 (1H, d, A of AB q, J = 13.5 Hz), 4.78 (1H, d, B of AB q, J = 13.4 Hz), 3.60 (1H, d, A of AB q, J = 18.31 Hz), 3.41 (1H, d, B of AB q, J = 18.11 Hz), 2.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 194.6 (s), 170.3 (s), 160.6 (s), 156.1 (s), 139.1 (s), 138.9 (s), 128.4, 128.1, 128.0, 127.7, 127.1, 124.6, 111.7 (s), 81.8 (d), 79.9 (d), 62.9 (t), 56.2 (d), 27.8(t), 20.5 (q). **Method B.** Lithium bromide (LiBr, 285 mg, 3.3 mmol) and copper(I) bromide (CuBr, 470 mg, 3.3 mmol) were added in one portion to a solution of benzhydryl 6α-ethynyl-6β-(trifluoromethanesulfonato)cephalosporanate (1.5 g, 2.5 mmol) in anhydrous THF (15 mL). The mixture was allowed to stir at room temperature for 5 min. The THF was removed *in vacuo*. The residue was dissolved in ether (20 mL), washed with water (1×, 10 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give yellow solid (1.30 g, 98% yield).

Benzhydryl 7-Vinylidenecephalosporanate (7). To a solution of benzhydryl 7-(α-bromovinylidene)cephalosporanate (2.4 g, 4.6 mmol) in a 1:5 mixture of anhydrous THF:MeOH (60 mL) was added NH_4Cl (0.98 g, 18.4 mmol) and Zn−Cu couple (0.6 g, 9.2 mmol). After 30 min of stirring at room temperature, the reaction mixture was concentrated. The residue was dissolved in ether (100 mL), washed with water (20 mL), dried (Na_2SO_4), concentrated, and chromatographed (1:1 hexane:CH_2Cl_2 and 1:3 hexane:CH_2Cl_2) to give white fluffy solid (1.45 g, 71% yield): R_f = 0.3 in CH_2Cl_2; IR ($CHCl_3$) 3010, 1985, 1790, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (10H, m), 7.0 (1H, s), 5.58 (2H, d, J = 13.4 Hz), 5.29 (1H, t, J = 1.88 Hz), 4.99 (1H, d, A of AB q, J = 13.35 Hz), 4.74 (1H, d, B of AB q, J = 13.3 Hz), 3.57 (1H, d, A of AB q, J = 18.2 Hz), 3.37 (1H, d, B of AB q, J = 18.3 Hz), 2.03 (3H, s); ^{13}C NMR ($CDCl_3$) δ 200.0 (s), 170.3 (s), 160.8 (s), 158.7 (s), 139.2 (s), 139.0 (s), 128.4, 128.0, 127.9, 127.7, 127.4, 127.0, 123.0, 105.7 (s), 85.1 (t), 79.7 (d), 63.0 (t), 56.6 (d), 27.8 (t), 20.5 (q). Anal. ($C_{25}H_{21}NO_5S$) C, H, N.

Benzhydryl 7α-Vinylidenecephalosporanate Sulfone (8). This compound was prepared from the sulfide **7** as described above for the preparation of **5** (yield = 55%, 0.590 g): R_f = 0.35 in 5% EtOAc in CH_2Cl_2; mp 155−156 °C; IR ($CHCl_3$) 3010, 1985, 1790, 1730, 1340, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (10H, m), 6.99 (1H, s), 5.70 (2H, dd, J = 1.65 Hz, J = 5.31 Hz), 5.33 (1H, s), 5.03 (1H, d, A of AB q, J = 14.02 Hz), 4.70 (1H, d, B of AB q, J = 14.01 Hz), 4.04 (1H, d, A of AB q, J = 18.12 Hz), 3.79 (1H, d, B of AB q, J = 18.40 Hz), 2.03 (3H, s); ^{13}C NMR ($CDCl_3$) δ 201.7 (s), 170.1 (s), 159.8 (s), 157.6 (s), 138.8 (s), 138.6 (s), 128.4, 128.2, 128.1, 127.5, 127.0, 124.0, 98.8 (s), 86.4 (t), 80.3 (d), 69.5 (d), 61.9 (t), 51.0 (t), 20.3 (q). Anal. ($C_{25}H_{21}NO_7S$) C, H, N.

Benzhydryl 7-[(*E*)-Benzylidene]cephalosporanate (11) and Benzhydryl 7-[(*Z*)-Benzylidene]cephalosporanate (9). To a solution of benzyl triphenylphosphonium bromide (11.44 g, 26.4 mmol) in anhydrous THF (50 mL) was added a solution of *n*-BuLi (14.5 mL, 29.0 mmol) at −78 °C. The mixture was stirred at room temperature for 30 min. The resulting red-colored solution was recooled to −78 °C and was added to a cold (−78 °C) solution of 7-oxocephalosporanate **3** (10.5 g, 24.0 mmol) in anhydrous THF (25 mL), and te mixture was stirred at −78 °C for 5 min. The cold reaction mixture was then poured into ice cold saturated NH_4Cl solution (25 mL), and the layers were separated. The aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with water (25 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography (CH_2Cl_2: hexane, 3:1) to give the *E*-isomer (0.83 g, 7%) and the *Z* -isomer (1.26 g, 10%) as white fluffy solids.

7(*E*)-Isomer: R_f = 0.60 in CH_2Cl_2; mp 59−61 °C; IR ($CHCl_3$) 3015, 1760, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (2H, m), 7.26 (13H, m), 6.93 (1H, s), 6.53 (1H, s), 4.99 (1H, s), 4.78 (1H, d, A of AB q, J = 13 Hz), 4.53 (1H, d, B of AB q, J = 13 Hz), 3.39 (1H, d, A of AB q, J = 18 Hz), 3.19 (1H, d, B of AB q, J = 18 Hz), 1.85 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.2 (s), 161.1 (s), 158.7 (s), 139.3 (s), 139.1 (s), 136.0(s), 134.0 (d), 133.1, 130.3, 128.6, 128.3, 128.0, 127.7, 127.0, 121.7 (s), 79.6 (d), 63.1 (t), 56.1 (d), 27.9 (t), 20.5 (q). Anal. ($C_{30}H_{25}NO_5S$) C, H, N.

7(*Z*)-Isomer: R_f = 0.50 in CH_2Cl_2; mp 45−47 °C; IR ($CHCl_3$) 3025, 1790, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (15H, m), 7.21

(1H, d, J = 1.18 Hz), 7.07 (1H, s), 5.50 (1H, d, J = 1.23 Hz), 5.00 (1H, d, A of AB q, J = 13 Hz), 4.75 (1H, d, B of AB q, J = 13 Hz), 3.65 (1H, d, A of AB q, J = 18 Hz), 3.41 (1H, d, B of AB q, J = 18 Hz), 2.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.3 (s), 161.0 (s), 160.2 (s), 139.3 (s), 139.1 (s), 135.8(s), 132.4 (d), 130.5, 129.7, 129.0, 128.3, 128.1, 127.9, 127.7, 127.0, 121.7(s), 79.7 (d), 63.1 (t), 57.7 (d), 28.0 (t), 20.5 (q); high-resolution mass spectrum for $[C_{30}H_{25}NO_5SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 534.1351, found 534.1352. Anal. ($C_{30}H_{25}NO_5S$) C, H, N.

Benzhydryl 7-[(*Z*)-Benzylidene]cephalosporanate Sulfone (10). This compound was prepared from the sulfide **9** (0.68 g, 1.3 mmol) as described for **5** to give a white solid (yield = 57%, 0.410 g): R_f = 0.40 in CH_2Cl_2; mp 61−63 °C; IR ($CHCl_3$) 3025, 2925, 1780, 1730, 1340, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42 (15H, m), 7.12 (1H, s), 6.98 (1H, s), 5.53 (1H, s), 4.95 (1H, d, A of AB q, J = 13 Hz), 4.65 (1H, d, B of AB q, J = 13 Hz), 4.04 (1H, d, A of AB q, J = 18 Hz), 3.77 (1H, d, B of AB q, J = 18 Hz), 1.96 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 159.9 (s), 159.7 (s), 138.8 (s), 138.7 (s), 134.12 (s), 131.6 (d), 131.0, 129.8, 129.1, 128.4, 128.2, 128.1, 127.6, 127.0, 126.7, 126.2, 121.8 (d), 80.3 (d), 71.7 (d), 691.9 (t), 51.6 (t), 20.3 (q); high-resolution mass spectrum for $[C_{30}H_{25}NO_7SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 566.1249, found 566.1262. Anal. ($C_{30}H_{25}NO_7S$) C, H, N.

Benzhydryl 7-[(*E*)-Benzylidene]cephalosporanate Sulfone (12). This compound was prepared from the sulfide **11** (0.51 g, 1.0 mmol) as described for **5** to give a white solid (0.350 g, yield = 65%): R_f = 0.27 in CH_2Cl_2; mp 194−196 °C; IR ($CHCl_3$) 2975, 1775, 1730, 1340, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.00 (2H, m), 7.41 (13H, m), 7.03 (1H, s), 6.94 (1H, s), 5.24 (1H, s), 5.04 (1H, d, A of AB q, J = 14 Hz), 4.70 (1H, d, B of AB q, J = 14 Hz), 4.05 (1H, d, A of AB q, J = 18 Hz), 3.77 (1H, d, B of AB q, J = 18 Hz), 2.05 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.3 (s), 160.1(s), 157.7 (s), 138.9 (s), 138.8 (s), 138.5(d), 132.5, 131.5, 131.0, 128.9, 128.6, 128.3, 127.7, 127.1, 126.7, 122.8 (s), 80.4 (d), 69.5 (d), 62.1 (t), 51.2 (t), 20.5 (q); high-resolution mass spectrum for $[C_{30}H_{25}NO_7SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 566.1249, found 566.1248. Anal. ($C_{30}H_{25}NO_7S$) C, H, N.

Benzhydryl 7-(Dibromomethylene)cephalosporanate (13). To the solution of Ph_3P (12.0 g, 45.8 mmol) in anhydrous CH_2Cl_2 (75 mL) was added CBr_4 (7.6 g, 22.9 mmol) in one portion at 0 °C. The mixture was stirred at room temperature for 30 min. The reaction mixture was then cooled to −78 °C, and a cold (−78 °C) solution of benzhydryl 7-oxocephalosporanate **3** (5.00 g, 11.4 mmol) in anhydrous CH_2Cl_2 (40 mL) was added. After 30 min of stirring at −78 °C, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2) to give a pale yellow solid (4.1 g, 61% yield): R_f = 0.55 in CH_2Cl_2; mp 58−60 °C; IR ($CHCl_3$) 3030, 1780, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (10H, m), 6.96 (1H, s), 5.19 (1H, s), 4.97 (1H, d, A of AB q, J = 13 Hz), 4.72 (1H, d, B of AB q, J = 13 Hz), 3.52 (1H, d, A of AB q, J = 18 Hz), 3.32 (1H, d, A of AB q, J = 18 Hz), 2.00 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.2 (s), 160.5 (s), 155.6 (s), 142.6 (s), 139.1 (s), 138.9 (s), 128.4, 128.0, 127.9, 127.0, 126.7, 125.2 (s), 92.6 (s), 79.9 (d), 63.0 (t), 60.1 (d), 27.0 (t), 20.5 (q). Anal. ($C_{24}H_{19}Br_2NO_5S$) C, H, N.

Benzhydryl 7-(Dibromomethylene)cephalosporanate Sulfone (14). This compound was prepared from the sulfide **15** as described above for **5** to yield a white solid (0.25 g, 79%): R_f = 0.50 in 2% EtOAc in CH_2Cl_2; mp 62−64 °C; IR ($CHCl_3$) 3030, 1800, 1740, 1350, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (10H, m), 6.95 (1H, s), 5.20 (1H, s), 5.03 (1H, d, A of AB q, J = 14 Hz), 4.68 (1H, d, B of AB q, J = 14 Hz), 4.02 (1H, d, A of AB q, J = 18 Hz), 3.77 (1H, d, B of AB q, J = 18 Hz), 2.02 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 159.6 (s), 154.8 (s), 138.8 (s), 138.7 (s), 135.2 (s), 128.6, 128.3, 127.5, 127.1, 126.4, 125.5 (s), 124.1 (s), 98.2 (s), 80.8 (d), 73.0 (d), 62.0 (t), 52.1 (t), 20.5 (q). Anal. ($C_{24}H_{19}Br_2NO_7S$) C, H, N.

Benzhydryl 7-[(*E*)-Bromomethylene]cephalosporanate (15). To a solution of 7-(dibromomethylene)cephalosporanate **13** (1.19 g, 2 mmol) in methanol (20 mL) and THF (10 mL) was added NH_4Cl (8.56 g, 16 mmol) in one portion at 0 °C. The mixture was stirred for 5 min. Zn/Cu (5.20 g, 8 mmol) was added in one portion and further stirred at room temperature for 30 min. The solvent was removed, and the residue was extracted with ether (2 × 20 mL). The obtained ether was washed with water (1 × 20 mL) and brine (1 × 10 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography (CH_2Cl_2) to give a white solid (0.86 g, 83% yield). R_f = 0.41 in CH_2Cl_2; mp 48−50 °C; IR ($CHCl_3$) 3025, 1780, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (10H, m), 6.96 (1H, s), 6.44 (1H, s), 5.05 (1H, s) 4.92 (1H, d, A of AB q, J = 13 Hz), 4.67 (1H, d, B of AB q, J = 13 Hz), 3.46 (1H, d, A of AB q, J = 18 Hz), 3.26 (1H, d, B of AB q, J = 18 Hz), 1.96 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.15 (s), 160.60 (s), 157.04 (s), 141.77 (s), 139.05 (s), 138.86 (s), 128.32, 127.97, 127.89, 127.49, 126.92, 123.30 (s), 107.94 (d), 79.82 (d), 62.90 (t), 58.02 (d), 27.68 (t), 20.42 (q). Anal. ($C_{24}H_{20}BrNO_5S$) C, H, N.

Benzhydryl 7-[(*E*)-Bromomethylene]cephalosporanate Sulfone (16). This compound was prepared from the corresponding sulfide **13** as described above for **5** to give a white solid (yield = 71%): R_f = 0.43 in 2% EtOAC in CH_2Cl_2; mp 80−82 °C; IR ($CHCl_3$) 3030, 1800, 1730, 1350, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (10H, m), 6.94 (1H, s), 6.91 (1H, s), 5.10 (1H, s), 5.00 (1H, d, A of AB q, J = 14 Hz), 4.67 (1H, d, B of AB q, J = 14 Hz), 3.97 (1H, A of AB q, J = 18 Hz), 3.69 (1H, d, B of AB q, J = 18 Hz), 1.99 (1H, s); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 159.7 (s), 156.3 (s), 138.7 (s), 138.6 (s), 134.0 (s), 128.4, 128.1, 127.3, 126.9, 125.7, 124.9 (s), 112.5 (d), 80.57 (d), 70.9 (d), 61.8 (t), 51.2 (t), 20.4 (q). Anal. ($C_{24}H_{20}BrNO_7S$) C, H, N.

Benzhydryl 7-[(*Z*)-(*tert*-(Butoxycarbonyl)methylene]-cephalosporanate (17). To a solution of benzhydryl 7-oxocephalosporanate **2** (4.0 g, 9.2 mmol) in anhydrous CH_2Cl_2 (40 mL) at −78 °C was added a solution of [(*tert*-butoxycarbonyl)-methylene]triphenylposphorane (3.45 g, 9.15 mmol in 40 mL CH_2Cl_2). The mixture was then stirred at −78 °C for 30 min. Acetic acid (1 mL) was added to quench the reaction, and the reaction mixture was concentrated and purified by column chromatography to give title compound as a pale yellow solid. (yield = 55%): R_f = 0.52 in 2% EtOAc in CH_2Cl_2; mp 48−50 °C; IR ($CHCl_3$) 3050, 1780, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (10H, m), 7.00 (1H, s), 6.39 (1H, s), 5.47 (1H, s), 5.00 (1H, d, A of AB q, J = 13.48 Hz), 4.77 (1H, d, B of AB q, J = 13.48 Hz), 3.62 (1H, d, A of AB q, J = 18 Hz), 3.38 (1H, d, B of AB q, J = 18 Hz), 2.02 (3H, s), 1.54 (9H, s); ^{13}C NMR ($CDCl_3$) δ 170.2 (s), 162.4 (s), 160.5 (s), 157.8 (s), 150.1, (s), 139.0 (s), 138.8 (s), 128.3, 128.0, 127.9, 127.5, 126.9, 125.0 (s), 119.9 (d), 82.9 (s), 79.7 (d), 62.8 (t), 57.5 (d), 28.0 (q), 27.9 (t), 20.4 (q). Anal. ($C_{29}H_{29}NO_7S$) H, N; C: calcd, 65.05; found, 64.50.

Benzhydryl 7-[(*Z*)-(*tert*-Butoxycarbonyl)methylene]-cephlosporanate Sulfone (18). This compound was prepared from the corresponding sulfide **17** as described above for **5** to give a white solid (yield = 73%): R_f = 0.68 in 5% EtOAc in CH_2Cl_2; mp 58−60 °C; IR ($CHCl_3$) 3025, 1800, 1730, 1350, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (10H, m), 6.98 (1H, s), 6.59 (1H, s), 5.58 (1H, s), 5.14 (1H, d, A of AB q, J = 14 Hz), 4.80 (1H, d, B of AB q, J = 14 Hz), 4.12 (1H, d, A of AB q, J = 18 Hz), 3.77 (1H, d, B of AB q, J = 18 Hz), 2.04 (3H, s), 1.52 (9H, s); ^{13}C NMR ($CDCl_3$) δ 170.0 (s), 161.5 (s), 159.4 (s), 157.1 (s), 142.3 (s), 138.6 (s), 138.5 (s), 128.8, 128.4, 128.3, 127.2, 127.0, 125.9 (s), 123.5 (d), 83.8 (s), 80.2 (d), 71.6 (d), 61.3 (t), 52.8 (t), 27.6 (q), 20.2 (q); high-resolution mass spectrum for $[C_{29}H_{29}NO_9SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 590.1461, found 590.1447. Anal. ($C_{29}H_{29}NO_9S$) C, H, N.

Benzhydryl 7-[(*Z*)-Formylmethylene]cephalosporanate (19). This compound was prepared from **2** and (triphenylphosphoranylidene)acetaldehyde using the procedure described for the preparation of compound **17** (yield = 46%): R_f = 0.37 in 2% EtOAc in CH_2Cl_2; mp 113−115 °C; IR ($CHCl_3$) 3050, 1780, 1730, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.80 (1H, d, J = 6.1 Hz), 7.34 (10H, m), 6.99 (1H, s), 6.60 (1H, d, J = 6.1 Hz), 5.45 (1H, s), 5.00 (1H, d, A of AB q, J = 13.51 Hz), 4.75 (1H, d, B of AB q, J = 13.55 Hz), 3.64 (1H, d, A of AB q, J = 18.59 Hz), 3.41 (1H, d, B of AB q, J = 18.61 Hz), 2.00 (3H, s); ^{13}C NMR ($CDCl_3$) δ 188.2 (d), 170.1 (s), 160.3 (s), 157.0 (s), 154.7 (s), 138.9 (s), 138.8 (s), 128.4, 128.1, 128.0, 127.6, 126.9, 126.7, 125.0 (s), 123.5 (d), 79.9 (d), 62.4 (t), 56.4 (d), 28.1 (t), 20.4 (q); high-resolution mass spectrum for $[C_{25}H_{21}NO_6SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 486.0987, found 468.0981. Minor product *E*-isomer; ^{1}H NMR ($CDCl_3$) d 10.28 (1H, d, J = 7.6 Hz), 7.34 (10H, m), 6.99 (1H, s), 6.26 (1H, d, J = 7.6 Hz), 5.28 (1H, s), 5.00 (1H, d, A of AB q, J = 13.5 Hz), 4.75 (1H, d, B of AB q, 13.5 Hz), J = 3.60 (1H, d, A of AB q, J = 18.6 Hz), 3.40

(1H, d, B of AB q, J = 18.6 Hz), 2.00 (3H, s). Anal. ($C_{25}H_{21}NO_6S$) C, H, N.

Benzhydryl 7-[(*Z*)-(2′-Pyridyl)methylene]cephalosporanate (20). To a solution of 2-picolyl chloride hydrochloride (13.1 g, 80 mmol) in water (20 mL) was added K_2CO_3 (11.0 g, 80 mmol). After the carbonate was completely dissolved, the solution was extracted with ether (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (1 × 30 mL), dried (Na_2SO_4), and concentrated to give picolyl chloride (9.2 g, 90%). Picolyl chloride (8.9 g, 70 mmol), triphenylphosphine (18.3 g, 70 mmol), and 1,4-dioxane (30 mL) were mixed and refluxed for 24 h. The reaction mixture was washed with ether (2 × 30 mL), and the remaining solid was dried *in vacuo* to give a white solid (25.5 g, 94%). A mixture of 2-picolyltriphenylphosphonium chloride (5.8 g, 15 mmol) and sodium amide (0.58, 15 mmol) in THF (15 mL) was stirred at room temperature for 30 min. The resulting brown suspension was cooled to −78 °C, a solution of benzhydryl 7-oxocephalosporanate **2** (6.6 g, 15 mmol) in THF (15 mL) was added in one portion and the mixture was stirred at −78 °C for 15 min. The reaction was quenched by the addition of saturated ammonium chloride solution (10 mL) and the reaction mixture extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (2 x 40 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography to obtain a yellow solid (2.9 g, 38%): R_f = 0.28 in 2% EtOAc in CH_2Cl_2; mp 181−183 °C; IR ($CHCl_3$) 3060, 1810, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.68 (1H, d), 7.72 (1H, t), 7.35(12H, m), 7.15 (1H, s), 7.10 (1H, s), 5.66 (1H, s), 4.96 (1H, d, A of AB q, J = 13 Hz), 4.73 (1H, d, B of AB q, J = 13 Hz), 3.63 (1H, d, A of AB q, J = 18 Hz), 3.63 (1H, D, B of AB q, J = 18 Hz), 2.01 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.3 (s), 161.0 (s), 160.2 (s), 151.6 (d), 150.1 (s), 140.6 (s), 139.3 (s), 139.1 (s), 136.6 (d), 128.3, 127.9, 127.8, 127.6, 127.2, 126.9, 125.8 (s), 123.9 (s), 123.5 (s), 79.5 (d), 63.0 (t), 58.5 (d), 28.0 (t), 20.5 (q); high-resolution mass spectrum for $[C_{29}H_{24}N_2O_5SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 535.1304, found 535.1300. Anal. ($C_{29}H_{24}N_2O_5S$) C, H, N.

Benzhydryl 7-[(*Z*)-(2′-Pyridyl)methylene]cephalosporanate Sulfone (21). This compound was prepared from the corresponding sulfide **21** (0.45 g, 0.88 mmol) as described for **5** to give a white solid (yield = 90%): R_f = 0.26 in 2% EtOAc in CH_2Cl_2; mp 120−122 °C; IR ($CHCl_3$) 2975, 2950, 1780, 1720, 1340, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.67 (1H, d), 7.71 (1H, t), 7.40 (13H, m), 7.00 (1H, s), 5.91 (1H, s), 5.14 (1H, d, A of AB q, J = 14 Hz), 4.80 (1H, B of AB q, J = 14 Hz), 4.11 (1H, d, A of AB q, J = 18 Hz), 3.78 (1H, d, B of AB q, J = 18 Hz), 2.05 (3H, s); high-resolution mass spectrum for $[C_{29}H_{24}N_2O_7SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 567.1202, found 567.1198. Anal. ($C_{29}H_{24}N_2O_7S$) C, H, N.

Benzhydryl 7-(Dichloromethylene)cephalosporanate (22). CCl_4 (2 mL, 20.7 mmol) was added into a solution of PPh_3 in anhydrous CH_3CN (50 mL), and the mixture was stirred at room temperature for 30 min. This solution was transferred into a solution of benzhydryl 7-oxocephalosporanate **2** (3.0 g, 8.9 mmol) in anhydrous CH_3CN (20 mL), and Zn/Cu (1.0 g, 15 mmol) was added. This reaction mixture was further stirred at room temperature for 40 min. The unreacted Zn/Cu was removed by filtration, and the filtrate was concentrated and purified by column chromatography (CH_2Cl_2) to yield a pale yellow solid (2.70 g, 78%): R_f = 0.73 in CH_2Cl_2; mp 48−50 °C; IR ($CHCl_3$) 3050, 1780, 1740, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (10H, m), 6.99 (1H, s) 5.29 (1H, s), 5.02 (1H, d, A of AB q, J = 13 Hz), 4.76 (1H, d, B of AB q, J = 13 Hz), 3.57 (1H, d, A of AB q, J = 18 Hz) 3.88 (1H, d, B of AB q, J = 18 Hz), 2.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.0 (s), 160.2 (s), 154.5 (s), 138.8 (s), 138.7 (s), 136.2 (s), 128.1, 127.7, 127.2, 126.6, 126.2, 124.7 (s), 123.6 (s), 79.8 (d), 62.8 (t), 57.4 (d), 26.9 (t), 20.3 (q); high-resolution mass spectrum for $[C_{24}H_{19}NO_5SCl_2Na]^+$, i.e. $[M + Na]^+$, m/z calcd 526.0259, found 526.0251. Anal. ($C_{24}H_{19}Cl_2NO_5S$) C, H, N.

Benzhydryl 7-(Dichloromethylene)cephalosporanate Sulfone (23). This compound was prepared from the corresponding sulfide **22** as described above for compound **5** to give a white solid (yield = 81%): R_f = 0.38 in 2% EtOAc in CH_2Cl_2; mp 64−66 °C; IR ($CHCl_3$) 3050, 1800, 1740, 1350, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (10H, m), 6.95 (1H, s), 5.28 (1H, s), 5.05 (1H, d, A of AB q, J = 14 Hz), 4.65 (1H, d, B of AB q, J = 14 Hz), 4.03 (1H, d, A of AB q, J = 18 Hz), 3.80 (1H, B of AB q, J = 18 Hz), 2.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.2 (s), 159.6 (s), 153.9 (s), 138.6 (s), 138.5 (s), 134.3 (s), 130.2 (s), 128.9, 128.6, 128.3, 127.6, 127.3, 127.1, 124.3 (s), 80.7 (d), 70.7 (d), 61.9 (t), 51.7 (t), 20.5 (q). Anal. ($C_{24}H_{19}Cl_2NO_7S$) C, H, N.

Benzhydryl 7-[(*Z*)-(Methoxycarbonyl)methylene]cephalosporanate (24). This compound was prepared from **2** and methyl (triphenylphosphoranylidene)acetate using the procedure described for the preparation of compound **17** (a pale yellow solid, 68%): R_f = 0.42 in 2% EtOAc in CH_2Cl_2; mp 47−49 °C; IR ($CHCl_3$) 3050, 1790, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (10H, m), 7.00 (1H, s), 6.49 (1H, s), 5.50 (1H, s), 5.00 (1H, d, A of AB q, J = 13.5 Hz), 4.76 (1H, d, B of AB q, J = 13.5 Hz), 3.84 (3H, s), 3.64 (1H, d, A of AB q, J = 18.8 Hz), 3.39 (1H, d, B of AB q, J = 18.8 Hz), 2.03 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.3, 163.8, 160.6, 157.5, 152.6, 139.2, 139.0, 128.6, 128.3, 127.9, 127.6, 127.3, 126.9, 125.5, 117.5, 79.9, 62.9, 57.9, 52.5, 27.9, 20.6. Anal. ($C_{26}H_{23}NO_7S$) C, H, N.

Benzhydryl 7-[(*Z*)-(Methoxycarbonyl)methylene]cephalosporanate sulfone (25). This compound was prepared from the corresponding sulfide **24** as described above for compound **5** (white solid, 84%): ^1H NMR ($CDCl_3$) δ 7.34 (10H, m), 6.95 (1H, s), 6.65 (1H, s), 5.51 (1H, s), 5.09 (1H, d, A of AB q, J = 14 Hz), 4.75 (1H, d, B of AB q, J = 14 Hz), 4.05 (1H, d, A of AB q, J = 10 Hz), 3.82 (3H, s), 3.79 (1H, B of AB q, J = 10 Hz), 2.02 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.3 (s), 163.7 (s), 160.6 (s), 157.6 (s), 152.5(s), 139.3 (s), 139.2 (s), 128.7, 128.5, 128.2, 128.1, 127.7, 127.0 (s), 126.6, 125.7, 117.6 (d), 79.8 (s), 78.2 (d), 62.9 (t), 57.8 (d),52.5, 27.9 (q), 20.6 (q). Anal. ($C_{26}H_{23}NO_9S$) C, H, N.

Benzhydryl 7-[(*Z*)-(Hydroxymethyl)methylene]cephalosporanate (26). To a solution of **19** (0.75 g, 1.62 mmol) in methanol (10 mL) and acetic acid (1 mL) was added $NaCNBH_3$ (0.51 g, 8.1 mmol) in one portion, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in EtOAc (25 mL) and water (10 mL). The aqueous layer was exacted with EtOAc (1 × 30 mL), and the combined organic layer was washed with water (1 × 30 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography to give a white solid (0.71g, 94%): R_f = 0.3 in 10% EtOAc in CH_2Cl_2; mp 58−60 °C; ^1H NMR ($CDCl_3$) δ 7.39 (10H, s), 7.01 (1H, s), 6.51 (1H, s), 5.29 (1H, s), 4.94 (1H, d, A of AB q, J = 13 Hz), 4.71 (1H, d, B of AB q, J = 13 Hz), 4.60 (1H, d, A of AB q, J = 20.83 Hz), 4.42 (1H, d, B of AB q, J = 20.22 Hz), 3.56 (1H, d, A of AB q, J = 18 Hz), 3.33 (1H, d, B of AB q, J = 18 Hz), 2.01 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.5 (s), 161.2 (s), 159.9 (s), 139.0 (s), 138.8 (s), 137.4 (s), 131.8 (d), 128.3, 128.0, 127.9, 127.6, 127.4, 126.8, 122.2 (s), 79.6 (d), 63.0 (t), 60.0 (t), 56.9 (d), 28.0 (t), 20.5 (q); high-resolution mass spectrum for $[C_{25}H_{23}NO_6SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 488.1144, found 488.1138. Anal. ($C_{25}H_{23}NO_6S$) C, H, N.

Benzhydryl 7-[(*Z*)-[(*N*-Methoxy-*N*-methylamino)carbonyl]methylene]cephalosporanate Sulfone (27). To a solution of benzhydryl 7-oxocephalosporanate **2** (1.0 g, 2.3 mmol) in anhydrous CH_2Cl_2 (20 mL) at −78 °C was added *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (0.73 g, 2.0 mmol). The mixture was stirred at −78 °C for 10 min, warmed to 0 °C, and further stirred for 15 min. Acetic acid (0.5 mL) was added to quench the reaction, and the reaction mixture was concentrated and purified by column chromatography (2% EtOAc in CH_2Cl_2) to give benzhydryl 7-[(*Z*)-[(*N*-methoxy-*N*-methylamino)carbonyl]methylene]cephalosporanate as a pale yellow solid (0.53 g, 51%): IR ($CHCl_3$) 3050, 1780, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (10H, m), 7.06 (1H, s), 7.00 (1H, s), 5.56 (1H, s), 4.96 (1H, d, A of AB q, J = 13 Hz), 4.75 (1H, d, B of AB q, J = 13 Hz), 3.75 (3H, s), 3.64 (1H, d, B of AB q, J = 19 Hz), 3.37 (1H, d, B of AB q, J = 19 Hz), 3.28 (3H, s), 2.01 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.4 (s), 163.1 (s), 160.8 (s), 158.5 (s), 151.2 (s), 139.2 (s), 139.0 (s), 128.5, 128.4, 128.1, 128.0, 127.8, 127.0, 124.8 (s), 115.6 (d), 79.8 (d), 63.0 (t), 62.4 (q), 58.0 (d), 32.2 (q), 28.1 (t), 20.6 (q).

This compound was oxidized to the corresponding sulfone as described above for **5** to give a white solid (yield = 68%): R_f = 0.44 in 25% EtOAc in CH_2Cl_2; mp 81−82 °C; IR ($CHCl_3$) 3050, 1800, 1740, 1360, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36

(10H, m), 7.28 (1H, s), 6.98 (1H, s), 5.72 (1H, s), 5.10 (1H, d, A of AB q, $J = 14$ Hz), 4.82 (1H, d, B of AB q, $J = 14$ Hz), 4.11 (1H, d, A of AB q, $J = 17$ Hz), 3.78 (1H, d, B of AB q, $J = 17$ Hz), 3.78 (3H, s), 3.31 (3H, s), 2.06 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 162.1 (s), 159.7 (s), 157.8 (s), 142.78 (s), 138.9 (s), 138.8 (s), 128.7, 128.4, 127.7, 127.4, 127.1, 126.9, 125.7 (s),, 119.3 (d), 80.3 (d), 72.3 (d), 62.5 (q), 61.8 (t), 52.9 (t), 32.3 (q), 20.5 (q); high-resolution mass spectrum for $[C_{27}H_{26}N_2O_9SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 577.1257, found 577.1247. Anal. ($C_{27}H_{26}N_2O_9S$) C, H, N.

Benzhydryl 7-[(*Z*)-Acetylmethylene]cephalosporanate (28). This compound was prepared from **2** and (triphenylphosphoranylidene)-2-propanone using the procedure described for the preparation of compound **17** (yield = 58%): $R_f = 0.29$ in 2% EtOAC in CH_2Cl_2; mp 49−50 °C; IR ($CHCl_3$) 3000, 1770, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (10H, m), 7.00 (1H, s), 6.48 (1H, s), 5.50 (1H, s), 5.00 (1H, d, A of AB q, $J = 13$ Hz), 4.77 (1H, d, B of AB q, $J = 13$ Hz), 3.63 (1H, d, A of AB q, $J = 19$ Hz), 3.38 (1H, d, B of AB q, $J = 19$ Hz). 2.39 (3H, s), 2.02 (3H, s); ^{13}C NMR ($CDCl_3$) δ 195.8 (s), 170.3 (s), 160.6 (s), 158.5 (s), 149.5 (s), 139.3 (s), 139.1 (s), 128.5, 127.8, 127.1, 126.9, 126.3, 125.6 (s), 122.7 (d), 79.8 (d), 63.0 (t), 58.0 (d), 30.9 (q), 28.0 (t), 20.7 (q). Anal. ($C_{26}H_{23}NO_6S$) C, H, N.

Benzhydryl 7-[(*Z*)-Acetylmethylene]cephalosporanate Sulfone (29). This compound was prepared from the corresponding sulfide **28** as described for **5** to give a white solid (yield = 79%). $R_f = 0.66$ in 25% EtOAc in CH_2Cl_2; mp 176−178 °C; IR ($CHCl_3$) 3050, 1800, 1730, 1350, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (10H, m), 6.99 (1H, s), 6.94 (1H, s), 5.64 (1H, s), 5.13 (1H, d, A of AB q, $J = 14$ Hz), 4.81 (1H, d, B of AB q, $J = 14$ Hz), 4.12 (1H, d, A of AB q, $J = 18$ Hz), 3.80 (1H, d, B of AB q, $J = 18$ Hz), 2.46 (3H, s), 2.07 (3H, s); ^{13}C NMR ($CDCl_3$) δ 194.7 (s), 170.1 (s), 159.5 (s), 157.5 (s), 141.2 (s), 138.7 (s), 138.6 (s), 128.6, 128.3, 127.5, 127.1, 126.8 (s), 125.3 (d), 80.5 (d), 72.2 (d), 61.7 (t), 53.1 (t), 31.0 (q), 20.5 (q); high-resolution mass spectrum for $[C_{26}H_{23}NO_8SNa]^+$, i.e. $[M + Na]^+$, m/z calcd 532.1042, found 532.1045. Anal. ($C_{26}H_{23}NO_8S$) C, H, N.

Benzhydryl 7-[(*Z*)-Cyanomethylene]cephalosporanate (30). This compound was prepared from (cyanomethylene)-triphenylphosphorane and **2** using a minor modification of the procedure described above for the preparation of **17** (the reaction was warmed to room temperature and stirred for an additional hour, while monitoring by TLC) (yield = 52%): ^{1}H NMR ($CDCl_3$) δ 7.6−7.3 (10H, m), 7.03 (1H, s), 6.12 (1H, s), 5.43 (1H, s), 5.08, 5.05 (1H, d, $J = 14$ Hz), 4.85, 4.82 (1H, d, $J = 14$ Hz), 3.67, 3.62 (1H, d, $J = 18.5$ Hz), 3.49, 3.44 (1H, d, $J = 18.5$ Hz), 2.06 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.4, 160.3, 158.3, 139.0, 128.9, 127.1, 113.1, 97.9, 80.2, 63.0, 56.9, 27.8, 20.7. Anal. ($C_{25}H_{20}N_2O_5S$) C, H, N.

Benzhydryl 7-[(*Z*)-Cyanomethylene]cephalosporanate Sulfone (31). This compound was prepared from the corresponding sulfide **30** using a procedure analogous to that described for **5** above (yield = 55%): ^{1}H NMR ($CDCl_3$) δ 7.6−7.2 (10 H, m), 6.89 (1H, s), 6.24 (1H, s), 5.29 (1H, s), 5.04, 5.01 (1H, d, $J = 14.5$ Hz), 4.70, 4.67 (1H, d, $J = 14.5$ Hz), 4.04, 3.99 (1H, d, $J = 18.5$ Hz), 3.79, 3.74 (1H, d, $J = 18.5$ Hz), 1.96 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.2, 159.2, 154.4, 149.7, 138.6, 138.5, 128.7, 127.7, 127.2, 112.3, 101.9, 80.9, 70.0, 61.9, 52.3, 20.6. Anal. ($C_{25}H_{20}N_2O_7S$) C, H, N.

Benzhydryl 7-{[(*E*)-Bromo-(*Z*)-methoxycarbonyl]methylidene}cephalosporanate (32). This compound was prepared from **2** and methyl bromo(triphenylphosphoranylidene)-acetate using the procedure described for the preparation of compound **17** (yield = 68%): ^{1}H NMR ($CDCl_3$) δ 7.6−7.2 (10 H, m), 6.85 (1H, s), 5.48 (1H, s), 4.98 4.95 (1H, d, $J = 14$ Hz), 4.76, 4.73 (1H, d, $J = 14$ Hz), 3.81 (3H, s), 3.57, 3.52 (1H, d, $J = 18.5$ Hz), 3.37, 3.32 (1H, d, $J = 14$ Hz), 2.02 (3H, s). Anal. ($C_{26}H_{22}BrNO_7S$) C, H, N.

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