Photochemical Conversion of β,β,β-Trichloroethyl 6-Diazopenicillanate into 6β-Thiolpenicillin Derivatives

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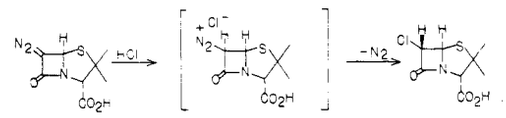
Irradiation of a mixture of β,β,β-trichloroethyl 6-diazopenicillanate (**3**) with either thiol acids or mercaptans leads predominantly to β-thiolpenicillanates in which the side chain nitrogen in the natural penicillins has been replaced with a sulfur atom. Evidence is presented for the formation of an azo intermediate which photochemically looses nitrogen giving rise to the aforementioned thiol derivatives. Sulfoxidation and thermal rearrangement afford deacetoxythiolcephalosporanates in good yield. In the case of the phenoxyacetyl or chloroacetyl derivatives **10** and **16** or **31** and **32**, the side chain can be cleaved under basic conditions giving the mercaptans **21** and **33** which were acylated by standard procedures.

The use of esters of 6-diazopenicillanic acid as a source of new antibacterial agents has recently been described;[1] however, the potential for these readily available, highly reactive intermediates has not been fully realized. As part of a general program to further investigate the properties of these esters, the irradiation of a mixture of β,β,β-trichloroethyl 6-diazopenicillanate (**3**) and either mercaptans or thiol acids was undertaken. We wish to report here the stereoselective conversion of **3** to analogues of penicillins and cephalosporins in which the side chain nitrogen has been replaced by a sulfur atom. We would also like to demonstrate their use as potential antibiotics.

Results and Discussion

The effect of the thiazolidine ring in penicillins in directing attack to the α face of the β-lactam ring is illustrated by the reaction of the diazo acid **1** with HCl.[2] Protonation takes place

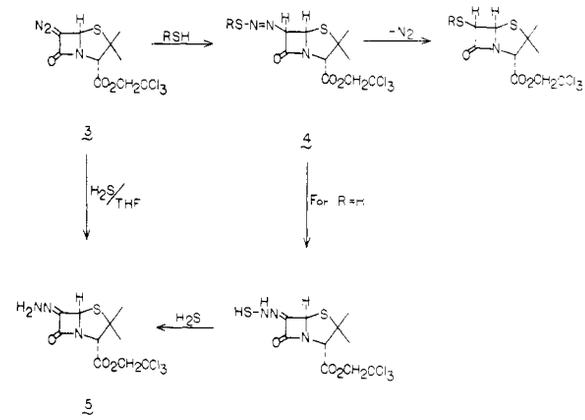


predominantly from the α face to give an intermediate in which the hydrogens at C-5 and C-6 of the β-lactam ring are cis (for numbering see figure **19**, Scheme II). Nucleophilic attack by the chloride ion, again from the α face, gives the product in which the hydrogens at C-5 and C-6 are now trans.

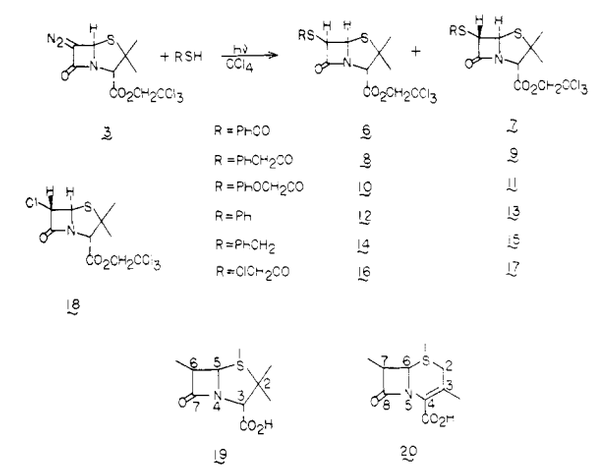
This directive effect can be an advantage. In the reaction of a mercaptan or thiol acid with a diazo ester such as **3**, if the sulfur attacks the nitrogen of the diazo moiety,[3] an azo intermediate will be formed in which the β-lactam hydrogens are cis. Loss of nitrogen with retention of configuration at C-6 will lead to a product with the desired cis stereochemistry[4] (Scheme I). Evidence suggesting that the sulfur will react at the nitrogen was observed in the reduction of **3** with hydrogen sulfide. Treatment of a THF solution of the diazo ester **3** with H_2S gave 66% yield of the hydrazone **5**. A possible mechanism is outlined in Scheme I.

A mixture of β,β,β-trichloroethyl 6-diazopenicillanate (**3**) and an excess of either thiobenzoic acid, phenylthiolacetic acid, or phenoxythiolacetic acid was irradiated in carbon tetrachloride with a medium-pressure Hanovia light source (Pyrex filter). Removal of the excess thiol acid with aqueous sodium bicarbonate and chromatography of the crude mixture on silicic acid gave the cis thiol esters **6**, **8**, and **10**, in 45–51% yield. In addition small quantities of the corresponding trans isomers **7**, **9**, and **11** were also isolated (Scheme II).

Scheme I



Scheme II



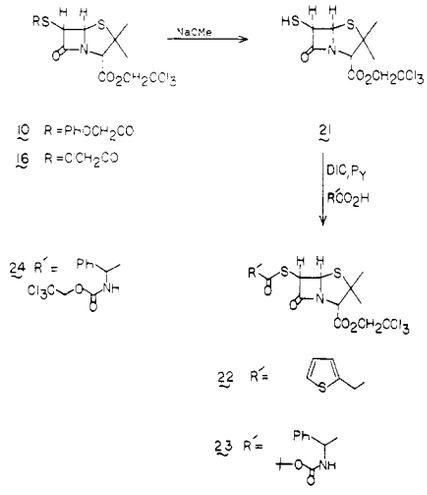
Irradiations were carried out below 20 °C. Above this temperature, there was significant to complete destruction of the acid-sensitive β-lactam ring. This lower temperature also diminishes the thermal reaction between **3** and the thiol acids leading to the undesired trans thiol esters (vide infra).

Structural assignments of the thiol esters are in complete agreement with the spectroscopic data (see Experimental Section). The stereochemistry at C-6 was assigned on the basis of the coupling between the C-5 and C-6 protons of the β-lactam ring.[5] The cis thiol esters had coupling constants of 4 Hz whereas the trans isomers had coupling constants of 2 Hz.

A mixture of **3** and thiophenol was irradiated. Chromatography on silicic acid gave the sulfides **12** and **13** as a mixture from which the cis sulfide **12** crystallized. Continuous crystallization of the mother liquors gave **12** in 56% yield. NMR analysis of the residual oil showed it to be the pure trans sulfide **13** (23%). In the same manner irradiation of a mixture of **3** and benzyl mercaptan gave, after extensive chromatography on silicic acid, the cis and trans sulfides **14** and **15** in 28 and 7% yields, respectively (Scheme II).

Attempts to prepare either **22** or **24** (Scheme III) by the

Scheme III



method just described were unsuccessful. Apparently irradiation of a mixture of **3** and a thiol acid which contains an additional functional group (and is therefore competitive in its nucleophilic character with the sulfur of the thiol acid) interferes with the reaction. A number of effective β-lactam antibiotics in the natural series (nitrogen analogues) contain such side chains so it was necessary to find a general route to these compounds.

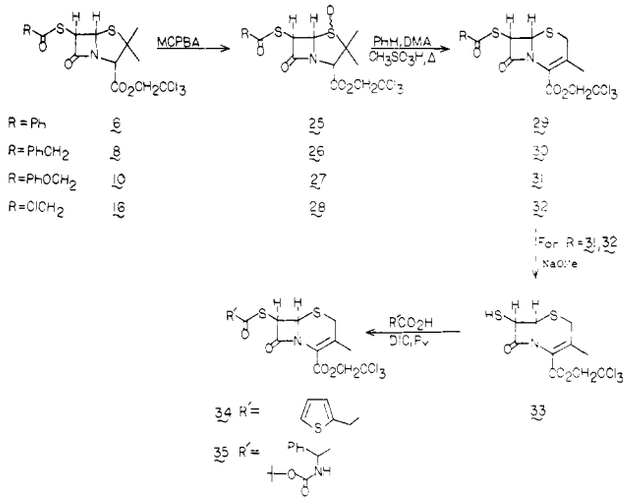
The most obvious method of preparing either **22** or **24** is by acylation of the mercaptan **21.** In general, the hydrolysis of a thiol ester under basic conditions would be expected to proceed smoothly. However, owing to the sensitivity of the β-lactam ring toward nucleophilic cleavage, it was anticipated that a thiol ester activated in the α position with an electron-withdrawing group might be required. An attempt to remove the phenylacetyl side chain from **8** by methanolysis at low temperature showed this to be the case. An NMR of the crude reaction mixture showed a complex mixture of components. However, with the phenoxy derivative **10,** which is activated relative to **8,** the reaction proceeded smoothly to give a mixture of the mercaptan **21** and methyl phenoxyacetate; the latter by-product had to be removed by chromatography (Scheme III). An activated thiol ester whose methyl ester could be removed under standard workup procedures was thus desired. For this reason, the chloroacetyl derivative **16** was prepared (Scheme II).

Irradiation of a mixture of **3** and chlorothiolacetic acid gave the thiol esters **16** and **17** in 49 and 4% yields, respectively. In addition, the trans chloride **18** was isolated in 9% yield as a crystalline material (Scheme II). This product arises from the reaction of **3** with HCl, a contaminant in chlorothiolacetic acid.[6]

Methanolysis of **16** gave the mercaptan **21** as a clear oil in 80% yield.[7] Acylation with D-α-*tert*-butoxycarboxamidophenylacetic acid[8] and thiophene-2-acetic acid in methylene chloride containing 1 equiv of *N,N'*-diisopropylcarbodiimide and pyridine gave, after column chromatography, the thiol esters **22** and **23** in 82 and 89% yields, respectively (Scheme III).

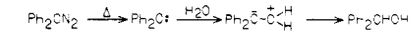
Oxidation of the cis thiol esters with *m*-chloroperbenzoic acid gave a mixture of sulfoxides[9] in high yield (Scheme IV).

Scheme IV



In the case of **25** and **26** the less polar sulfoxide (by TLC) crystallized from the crude mixture. Rearrangement of either the pure sulfoxide or the crude reaction mixture by the method originally described by Morin and co-workers[10] gave the deacetoxythiolcephalosporanates **29–32** in 40–90% yields. Methanolysis of either **31** or **32** gave the mercaptan **33** in 80% yield. Acylation as previously described for **22** and **23** gave the thiol esters **34** and **35** in 82% yield (Scheme IV).

The photochemical and thermal decomposition of diazo compounds has been studied extensively.[11] Bethell and coworkers[12] have shown that in the thermal decomposition of diphenyldiazomethane in aqueous acetonitrile an intermediate carbene reacts with the oxygen of water, giving an ylide which subsequently rearranges to diphenylmethanol. Inser-



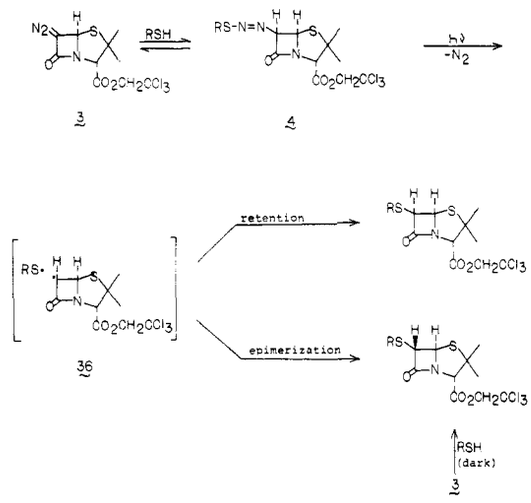
tion into an S–H bond has been reported[13] in the photolysis of bis(phenylsulfonyl)diazomethane in the presence of *n*-butyl mercaptan. Such a carbene "insertion" reaction, although possible, was considered unlikely in the case of **3.**

Light-induced formation of a carbene in **3** in the presence of either a mercaptan or thiol acid would lead to the corresponding sulfides and thiol esters. However, if a sulfonium ylide was formed it was believed that an intramolecular proton transfer,[14] giving rise to the thermodynamically more stable trans isomer, would be favored over an intermolecular proton transfer from the α face of the β-lactam ring which would give the cis isomer.

Further evidence against the formation of a carbene was observed in the irradiation of a carbon tetrachloride solution of **3** under an atmosphere of helium in the absence of any nucleophile. If a carbene were formed, such conditions should give rise to products which no longer contain the diazo group. After irradiation, NMR analysis of the crude reaction showed **3** as the only identifiable material.

There is evidence supporting the mechanism outlined in Scheme V. The cis stereochemistry of the β-lactam hydrogens is consistent with attack of the sulfur on the nitrogen with protonation at C-6 occurring from the α face of the β-lactam to give the cis azo ester **4.** Photochemical elimination of nitrogen with retention of configuration at C-6 will give the cis isomer.[15] The trans isomer can result from epimerization prior to combination of the diradical **36** or related species, (Scheme

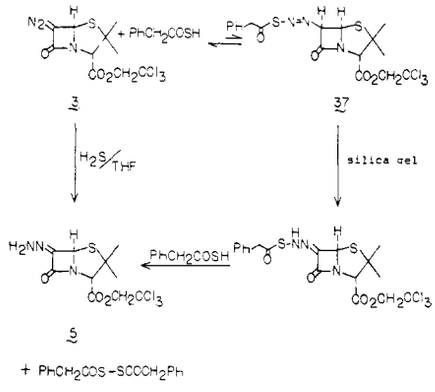
Scheme V



V) or from a thermal reaction between 3 and the thiol acid or mercaptan. In control experiments (no light) small amounts of the trans isomers were detected in an NMR of the crude reaction mixture.

Although isolation of an azo ester was not possible, its existence has been demonstrated. A TLC taken immediately after mixing 3 and phenylthiolacetic acid[16] in carbon tetrachloride showed two new components in addition to 3 and the thiol acid. One component, which is less polar than 3, was identical with diphenylacetyl disulfide 38 (Scheme VI) isolated as a crystalline material in a large-scale photolysis. The other component, more polar than 3, was identical with the hydrazone 5, previously prepared by the reduction of 3 with hydrogen sulfide (vide supra). After removal of the thiol acid from the aforementioned solution of 3 and phenylthiolacetic acid with aqueous sodium bicarbonate, conditions which were shown not to destroy either the disulfide or the hydrazone, a TLC showed only one spot corresponding to the diazo ester 3 and no detectable amounts of either the disulfide or the hydrazone.

Scheme VI



An explanation for the above observation is outlined in Scheme VI. An equilibrium exists between the diazo and azo esters which react on the surface of the silica gel (TLC sheets) giving the hydrazone 5 and the disulfide 38. Removal of the thiol acid with base destroys the equilibrium leaving only the diazo ester 3. It was not possible to observe 37 by either NMR or UV, showing that the equilibrium is largely in favor of 3.

Benzoyl disulfide, diphenylacetyl disulfide, and diphenoxyacetyl disulfide were isolated in large-scale photolyses of 3 and the corresponding thiol acids. The formation of these disulfides is not entirely clear.[17] Reduction of 3 is catalyzed by silica gel (vide supra). During the photolyses (10–20 h) reduction may still occur but at a slower rate, giving the disulfides and the hydrazone 5, the latter of which has been shown to be very sensitive to the conditions of the reaction and is presumably destroyed.

After removal of the protective group(s) (see Experimental Section) the free acids were tested in vitro for bioactivity. Minimum inhibitory concentrations (MIC) values in μg/mL for 6, 8, and 10 against *Bacillus subtilis* ATCC 6051 were 50, <0.4 and <0.4, respectively; 31 against *Staphylococcus aerus* A 100, *Staphylococcus pyogenes* Pen R, and *Aerobacter aerogenes* (50); 29 against *Staphylococcus aerus* A 100, *Staphylococcus pyogenes* Pen R, *Streptococcus fecalis*, and *Proteus mirabilis* (50) and against *Bacillus subtilis* ATCC 6051 (25).

Experimental Section

Melting points and boiling points are uncorrected; melting points were determined on a Fisher-Johns melting point apparatus. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Associates T-60 spectrophotometer and are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Infrared spectra (IR) were recorded on a Perkin-Elmer 237 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Routine thin layer chromatographies were run on Baker-flex silica gel 1B-F TLC sheets. For analytical TLC work solutions were applied with Drummond "microcaps" disposable micropipets. Preparative thick layer chromatographies were performed on EM Reagents precoated silica gel 60 F-254 (2-mm thickness). Column chromatography was performed with Mallinckrodt silicic acid (100 mesh). Irradiations were carried out in Pyrex flasks in an enclosed 28 × 38 × 87 cm wood box with the Hanovia 450-W medium-pressure lamp suspended horizontally above the flask. Solutions were flushed for 30 min with a slow stream of helium which was continued throughout the irradiations.

β,β,β-Trichloroethyl 6-diazopenicillanate (3) was prepared by the method of Sheehan and co-workers.[18]

Phenylthiolacetic acid, phenoxythiolacetic acid, and thiophene-2-thiolacetic acid were prepared by the method of Sjöberg.[19]

Chlorothiolacetic acid was prepared by the method of Arndt and Bekir.[6]

Thiophene-2-acetic acid was obtained from Research Organic/Inorganic Chemical Corp., Belleville, N.J.

Thiophene-2-acetyl chloride was prepared according to the literature.[20]

D-α-β,β,β-Trichloroethyloxycarboxamidophenylacetic acid[8] and D-α-*tert*-butoxycarboxamidophenylacetic acid[21] were prepared according to the literature.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Thiobenzoic Acid. A solution of 2.00 g (5.58 mmol) of 3 and 3.48 g (27.8 mmol) of thiobenzoic acid in 150 mL of carbon tetrachloride was irradiated with a Hanovia 450-W medium-pressure lamp (Pyrex filter) under an atmosphere of helium at 18 °C for 8 h. The solution was washed with 5% aqueous $NaHCO_3$ and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residual oil was submitted to column chromatography on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave benzoyl disulfide (163.8 mg) as a white, crystalline material. Trituration with ether gave the pure disulfide: mp 130.0–132.0 °C (lit.[22] mp 129–130 °C); NMR ($CDCl_3$) δ 7.0–8.2 (m, 10 H).

Isolation of a slower moving fraction gave the trans thiol ester 7 in 4% yield as a light brown oil. Upon standing the oil crystallized. Recrystallization from ether–petroleum ether gave an analytical sample: mp 69.0–72.0 °C; IR ($CHCl_3$) 1780 and 1675 cm^{-1}; NMR ($CDCl_3$ δ 1.65 (s, 3 H), 1.82 (s, 3 H), 4.65 (s, 1 H), 4.75 (s, 2 H), 5.02 (d, 1 H, J = 2.0 Hz), 5.20 (d, 1 H, J = 2.0 Hz), 7.0–8.0 (m, 5 H).

Anal. Calcd for $C_{17}H_{16}NO_4Cl_3S_2$: C, 43.56; H, 3.44; N, 2.99; Cl, 22.69; S, 13.68. Found: C, 43.80; H, 3.45; N, 2.93; Cl, 22.61; S, 13.40.

Isolation of the slowest moving fraction furnished a light brown oil in 51% yield which crystallized on standing. Recrystallization from ether gave the analytically pure cis thiol ester 6 as a white, crystalline material: mp 103.5–104.0 °C; IR ($CHCl_3$) 3010, 2960, 1780, and 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.73 (s, 3 H), 4.53 (s, 1 H), 4.68 (s, 2 H), 5.47 (d, 1 H, J = 4.0 Hz), 5.60 (d, 1 H, J = 4.0 Hz), 7.0–8.0 (m, 5 H).

Anal. Calcd for $C_{17}H_{16}NO_4Cl_3S_2$: C, 43.56; H, 3.44; N, 2.99; Cl, 22.69; S, 13.68. Found: C, 43.20; H, 3.81; N, 2.84; Cl, 22.46; S, 13.66.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Phenylthiolacetic Acid. In the same manner as described above diphenylacetyl disulfide (115 mg) was isolated as a crystalline material. Recrystallization from ether–petroleum ether gave the pure disulfide: mp 61.0–62.0 °C (lit.[23] mp 62 °C); IR ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (s, 4 H), 7.10 (s, 10 H).

Isolation of a slower moving fraction gave the trans thiol ester **9** in 3% yield as a light brown oil: IR ($CHCl_3$) 1780 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.73 (s, 3 H), 3.83 (s, 2 H), 4.58 (s, 1 H), 4.70 (s, 2 H), 4.80 (d, 1 H, J = 2.0 Hz), 5.05 (d, 1 H, J = 2.0 Hz), 7.13 (s, 5 H).

Isolation of the slowest moving fraction furnished a light brown oil in 50% yield which crystallized on standing. Recrystallization from ether–petroleum ether gave the analytically pure cis thiol ester **8** as a white, crystalline solid: mp 83.0–84.0 °C; IR ($CHCl_3$) 3005, 2955, 1770, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.70 (s, 3 H), 3.83 (s, 2 H), 4.53 (s, 1 H), 4.73 (s, 2 H), 5.33 (d, 1 H, J = 4.0 Hz), 5.55 (d, 1 H, J = 4.0 Hz), 7.18 (s, 5 H).

Anal. Calcd for $C_{18}H_{18}NO_4Cl_3S_2$: C, 44.78; H, 3.76; N, 2.90; Cl, 22.03; S, 13.28. Found: C, 44.70; H, 3.60; N, 2.86; Cl, 22.10; S, 13.59.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Phenoxythiolacetic Acid. In the same manner as described above diphenoxyacetal disulfide (58 mg) was isolated as a crystalline material. Recrystallization from methylene chloride–petroleum ether gave the analytically pure disulfide: mp 105.5–107.0 °C; IR ($CHCl_3$) 3010 and 1725 cm^{-1}; NMR ($CDCl_3$) δ 4.83 (s, 4 H), 6.7–7.7 (m, 10 H).

Anal. Calcd for $C_{16}H_{14}O_4S_2$: C, 57.47; H, 4.22; S, 19.18. Found: C, 57.36; H, 4.22; S, 19.23.

Isolation of a slower moving fraction furnished a light brown oil in 5% yield which crystallized on standing. Recrystallization from methylene chloride–ether–petroleum ether gave the analytically pure trans thiol ester **11**: mp 90.0–91.0 °C; IR ($CHCl_3$) 1775 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.77 (s, 3 H), 4.63 (s, 1 H), 4.70 (s, 2 H), 4.73 (s, 2 H), 4.87 (d, 1 H, J = 2.0 Hz), 5.12 (d, 1 H, J = 2.0 Hz), 6.7–7.7 (m, 5 H).

Anal. Calcd for $C_{18}H_{18}NO_5Cl_3S_2$: C, 43.34; H, 3.64; N, 2.81; Cl, 21.32; S, 12.86. Found: C, 43.31; H, 3.70; N, 2.83; Cl, 21.47; S, 12.83.

Isolation of the slowest moving fraction furnished the cis thiol ester **10** in 45% yield as a light brown oil: IR ($CHCl_3$) 1775 and 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.67 (s, 3 H), 4.60 (s, 1 H), 4.73 (s, 2 H), 4.80 (s, 2 H), 5.43 (d, 1 H, J = 4.0 Hz), 5.70 (d, 1 H, J = 4.0 Hz), 6.8–7.6 (m, 5 H).

Anal. Calcd for $C_{18}H_{18}NO_5Cl_3S_2$: C, 43.34; H, 3.64; N, 2.81; Cl, 21.32; S, 12.86. Found: C, 43.04; H, 3.68; N, 2.90; Cl, 21.60; S, 13.12.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Thiophenol. A solution of 1.00 g (2.79 mmol) of **3** in 65 mL of CCl_4 was cooled to 8–10 °C before 1.4 mL (13.7 mmol) of thiophenol in 10 mL of CCl_4 was added dropwise over 5 min. The solution was irradiated with a Hanovia 450-W medium-pressure lamp (Pyrex filter) under an atmosphere of helium at ~10 °C for 20 h. The solvent was removed under reduced pressure and the residue chromatographed on silicic acid using mixtures of methylene chloride–carbon tetrachloride as an eluent. After removal of the excess thiophenol the cis and trans sulfides **12** and **13** were isolated as a mixture from which the cis sulfide crystallized. Continuous crystallization of the mother liquors from methylene chloride–ether gave 56% yield of the cis sulfide **12** and 23% yield of an oil which was shown by NMR analysis to be the pure trans sulfide **13**.

Recrystallization of **12** from methylene chloride–ether gave an analytically pure sample: mp 122.0–123.0 °C; IR ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 4.60 (s, 1 H), 4.73 (s, 2 H), 4.77 (d, 1 H, J = 4.0 Hz), 5.57 (d, 1 H, J = 4.0 Hz), 7.0–7.7 (m, 5 H).

Anal. Calcd for $C_{16}H_{15}NO_3Cl_3S_2$: C, 43.60; H, 3.66; N, 3.18; Cl, 24.13; S, 14.55. Found: C, 43.53; H, 3.88; N, 3.20; Cl, 24.30; S, 14.46.

Trans Sulfide 13: IR ($CHCl_3$) 1775 and 1765 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.78 (s, 3 H), 4.53 (d, 1 H, J = 2.0 Hz), 4.70 (s, 1 H), 4.80 (s, 2 H), 5.28 (d, 1 H, J = 2.0 Hz), 7.2–7.7 (m, 5 H).

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Benzyl Mercaptan. A solution of 2.00 g (5.58 mmol) of **3** and 3.25 mL (27.6 mmol) of benzyl mercaptan in 150 mL of carbon tetrachloride was irradiated with a Hanovia 450-W medium-pressure lamp (Pyrex filter) under an atmosphere of helium at 38–40 °C for 22 h. The solvent was removed under reduced pressure and the residue chromatographed on silicic acid using mixtures of methylene chloride–carbon tetrachloride as an eluent. Isolation of the faster moving fraction furnished the trans sulfide **15** as a light brown oil: IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 3 H), 1.70 (s, 3 H), 3.83 (s, 2 H), 4.12 (d, 1 H, J = 2.0 Hz), 4.63 (s, 1 H), 4.73 (s, 2 H), 4.92 (d, 1 H, J = 2.0 Hz), 7.22 (s, 5 H).

Isolation of the slower moving fraction furnished an oil which crystallized on standing. Recrystallization from methylene chloride–petroleum ether gave the analytically pure cis sulfide **14**: mp 82.0–83.0 °C; IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.80 (s, 3 H), 3.87 (s, 2 H), 4.30 (d, 1 H, J = 4.0 Hz), 4.53 (s, 1 H), 4.73 (s, 2 H), 5.33 (d, 1 H, J = 4.0 Hz), 7.22 (s, 5 H).

Some of the fractions collected between pure **14** and **15** were mixtures. The total yield of the trans sulfide **15** (weight in mixtures determined from NMR integration) was 7%. The yield of the cis sulfide **14** was 28%.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Chlorothiolacetic Acid. A solution of 2.0 g (5.58 mmol) of **3** in 180 mL of carbon tetrachloride was cooled to ~3 °C before chlorothiolacetic acid (3.08 g, 27.9 mmol) in 20 mL of carbon tetrachloride was added dropwise over 30 min. The solution was irradiated with a Hanovia 450-W medium-pressure lamp (Pyrex filter) under a helium atmosphere at 3–5 °C for 15 h. The solution was washed with 5% aqueous $NaHCO_3$ and dried ($MgSO_4$) and the solvent removed under reduced pressure. The residual oil was submitted to column chromatography on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave the trans chloride **18** (84.2 mg, 8%) as a crystalline material. Recrystallization from methylene chloride–petroleum ether gave an analytically pure sample: mp 110.0–111.0 °C; IR ($CHCl_3$) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (s, 3 H), 1.73 (s, 3 H), 4.67 (s, 1 H), 4.81 (s, 3 H, $-CH_2CCl_3$ + 1 β-lactam H), 5.53 (d, 1 H, J = 2.0 Hz).

Anal. Calcd for $C_{10}H_{11}NO_3Cl_4S$: C, 32.72; H, 3.02; N, 3.82; Cl, 38.63; S, 8.74; Found: C, 32.77; H, 3.01; N, 3.81; Cl, 38.45; S, 8.66.

Isolation of a slower moving fraction gave the trans thiol ester **17** (106 mg, 4%) as an oil: IR ($CHCl_3$) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.75 (s, 3 H), 4.18 (s, 2 H), 4.62 (s, 1 H), 4.73 (s, 2 H), 4.82 (d, 1 H, J = 2.0 Hz), 5.13 (d, 1 H, J = 2.0 Hz).

Isolation of the slowest moving fraction gave 1.20 g (49%) of the cis thiol ester **16** as an oil: IR ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 4.22 (s, 2 H), 4.53 (s, 1 H), 4.73 (s, 2 H), 5.30 (d, 1 H, J = 4.0 Hz), 5.58 (d, 1 H, J = 4.0 Hz).

Synthesis of D-α-β,β,β-Trichloroethyloxycarboxamidophenylthiolacetic Acid. A mixture of 547 mg (1.67 mmol) of D-α-β,β,β-trichloroethyloxycarboxamidophenylacetic acid, 250 μL (3.44 mmol) of thionyl chloride, and 10 mL of dry benzene was refluxed overnight. Removal of the solvent and excess thionyl chloride under reduced pressure gave D-α-β,β,β-trichloroethyloxycarboxamidophenylacetyl chloride as a light brown oil: IR ($CHCl_3$) 1790 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.70 (s, 2 H), 5.50 (d, 1 H, J = 7.0 Hz), 5.6–6.1 (m, 1 H), 7.23 (s, 5 H).

The acid chloride in 10 mL of methylene chloride was added dropwise to a hydrogen sulfide saturated solution of pyridine at 0 °C. The solution was stirred at 0 °C for 1.5 h and at room temperature for 2 h. The solution was partitioned between methylene chloride and ice water. The aqueous layer was acidified with concentrated HCl. The organic layer was separated and extracted with aqueous $NaHCO_3$. Separation of the organic layer, partitioning the aqueous layer with methylene chloride, acidification with concentrated HCl, separation of the organic layer, drying ($MgSO_4$) and removal of the solvent under reduced pressure gave D-α-β,β,β-trichloroethyloxycarboxamidophenythiolacetic acid as a clear oil: NMR ($CDCl_3$) δ 4.67 (s, 2 H), 5.2–5.5 (m, 2 H, –SH and PhH–), 5.8–6.5 (m, 1 H), 7.17 (s, 5 H).

Synthesis of β,β,β-Trichloroethyl 6β-Mercaptopenicillanate (21). Sodium methoxide (43 mg, 0.80 mmol) in 20 mL of anhydrous methanol was added dropwise over 2 h to a stirred solution at −78 °C (CO_2–acetone) of 349 mg (0.79 mmol) of β,β,β-trichloroethyl 6β-(chloroacetylthio)penicillanate (**16**) in 30 mL of anhydrous methanol. After the addition the stirring was continued at −78 °C for 5.5 h. The CO_2–acetone bath was replaced with a CO_2–acetonitrile bath and the stirring continued at −50 to −65 °C for 3.5 h. Methylene chloride was added and the solution washed with ice-cold 10% HCl and 5% $NaHCO_3$ The organic solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residual oil was submitted to column chromatography on silicic acid using a 1:1 mixture (v/v) of methylene chloride– carbon tetrachloride as an eluent. The mercaptan **21** (229 mg, 80%) was isolated as an oil: IR (neat) 2955, 2550, and 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (s, 3 H), 1.80 (s, 3 H), 2.48 (d, 1 H, J = 21 Hz), 4.40–7.73 (m, 2 H, H-3 and H-6), 4.79 (s, 2 H), 5.60 (d, 1 H, J = 4.0 Hz).

Synthesis of β,β,β-Trichloroethyl 6β-(Thiophene-2-acetylthio)penicillanate (22). A solution of 120 μL (0.76 mmol) of *N,N*-

diisopropylcarbodiimide in 10 mL of methylene chloride was added dropwise over 30 min to an ice-cold solution of 108 mg (0.76 mmol) of thiophene-2-acetic acid, 61 μL (0.76 mmol) of pyridine, and 273 mg (0.75 mmol) of the mercaptan **21** in 50 mL of methylene chloride. After the addition the solution was stirred overnight at room temperature. Extraction of the solution with ice-cold 10% HCl and aqueous $NaHCO_3$, drying ($MgSO_4$) of the organic solution, and removal of the solvent under reduced pressure gave an oily solid (solid due to urea formed as by-product) which was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the major fraction gave the thiol ester **22** as an oil (325 mg, 89%) which crystallized on standing. Recrystallization from ether–petroleum ether gave an analytically pure sample: mp 86.0–87.0 °C; IR ($CHCl_3$) 1775 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 4.07 (s, 2 H), 4.55 (s, 1 H), 4.75 (s, 2 H), 5.32 (d, 1 H, J = 4.0 Hz), 5.67 (d, 1 H, J = 4.0 Hz), 6.7–7.3 (m, 3 H).

Anal. Calcd for $C_{16}H_{16}NO_4Cl_3S_3$: C, 39.31; H, 3.30; N, 2.86; Cl, 21.76; S, 19.68. Found: C, 39.49; H, 3.36; N, 2.78; Cl, 21.72; S, 19.58.

Synthesis of β,β,β-Trichloroethyl 6β-(D-α-*tert*-Butoxycarboxamidophenylacetylthio)penicillanate (23). In the same manner as described for **22** the thiol ester **23** was isolated as an oil (839 mg, 88%) after purification by column chromatography on silicic acid using 1% ether–methylene chloride (v/v) as an eluent: IR (neat) 3350, 2975, 1775, 1720, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 9 H), 1.60 (s, 3 H), 1.70 (s, 3 H), 4.50 (s, 1 H), 4.72 (s, 2 H), 5.2–5.6 (m, 4 H), 7.17 (s, 5 H).

Synthesis of β,β,β-Trichloroethyl 6β-(Phenylcarbothio)penicillanate 1-Oxide (25). A solution of *m*-chloroperbenzoic acid (454 mg, 2.63 mmol) in 20 mL of chloroform was added dropwise over 30 min to an ice-cold solution of the sulfide **6** (1.24 g, 2.64 mmol) in 50 ml of chloroform. After the addition the solution was stirred at 0 °C for 2 h, washed with aqueous $NaHCO_3$ and dried ($MgSO_4$) and the solvent removed under reduced pressure. Trituration of the residual oil with ether gave the sulfoxide **25** (1.04 g, 81%) as a crystalline material which was shown by NMR analysis to be predominantly one isomer (less polar isomer by TLC on silica gel–CH_2Cl_2). Recrystallization from methylene chloride–petroleum ether gave the analytically pure sulfoxide **25** (less polar) as white needles: mp 178.0–179.0 °C; IR ($CHCl_3$) 3005, 1805, 1760, and 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.80 (s, 3 H), 4.63 (d, 1 H, J = 12.0 Hz), 4.77 (s, 1 H), 5.03 (d, 1 H, J = 12.0 Hz), 5.30 (d, 1 H, J = 4.0 Hz), 6.03 (d, 1 H, J = 4.0 Hz), 7.2–8.2 (m, 5 H).

Anal. Calcd for $C_{17}H_{16}NO_5Cl_3S_2$: C, 42.12; H, 3.33; N, 2.89; Cl, 21.94; S, 13.23. Found: C, 42.12; H, 3.26; N, 2.87; Cl, 21.97; S, 13.21.

Synthesis of β,β,β-Trichloroethyl 6β-(Phenylacetylthio)-penicillanate 1-Oxide (26). A solution of *m*-chloroperbenzoic acid (180 mg, 1.04 mmol) in 25 mL of chloroform was added dropwise over 2 h to an ice-cold solution of the sulfide **8** (483 mg, 1.04 mmol) in 50 mL of chloroform. After the addition, the solution was stirred at 0 °C for 2 h, washed with aqueous $NaHCO_3$, and dried ($MgSO_4$) and the solvent removed under reduced pressure. Crystallization of the residual oil from methylene chloride–petroleum ether gave the sulfoxide **26** (139 mg, 27%, less polar isomer by TLC, (CH_2Cl_2) as white needles: mp 164.0–166.0 °C; IR ($CHCl_3$) 1805, 1760, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.77 (s, 3 H), 3.87 (s, 2 H), 4.61 (d, 1 H, J = 12.0 Hz), 4.70 (s, 1 H), 5.00 (d, 1 H, J = 12.0 Hz), 5.15 (d, 1 H, J = 4.0 Hz), 5.70 (d, 1 H, J = 4.0 Hz), 7.30 (s, 1 H).

Anal. Calcd for $C_{18}H_{18}NO_5Cl_3S_2$: C, 43.34; H, 3.64; N, 2.81; Cl, 21.32; S, 12.86. Found: C, 43.42; H, 3.50; N, 2.74; Cl, 21.49; S, 12.83.

The mother liquor from the aforementioned crystallization was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the faster moving fraction gave an additional 189 mg of the sulfoxide **26** (total yield of **26** was 63%). Isolation of the slower moving fraction gave the isomeric sulfoxide **26** (144 mg, 28%) as a crystalline material. Recrystallization from CH_2Cl_2–petroleum ether gave the analytically pure sample as white needles: mp 125.0–126.5 °C; IR ($CHCl_3$) 1800, 1775, 1710, and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.67 (s, 3 H), 3.90 (s, 2 H), 4.52 (s, 1 H), 4.63 (d, 1 H, J = 12.0 Hz), 4.80 (d, 1 H, J = 4.0 Hz), 4.97 (d, 1 H, J = 12.0 Hz), 5.30 (d, 1 H, J = 4.0 Hz), 7.32 (s, 5 H).

Anal. Calcd for $C_{18}H_{18}NO_5Cl_3S_2$: C, 43.34; H, 3.64; N, 2.81; Cl, 21.32; S, 12.86. Found: C, 43.27; H, 3.55; N, 2.83; Cl, 21.38; S, 12.75.

Synthesis of β,β,β-Trichloroethyl 7β-(Phenylcarbothio)deacetoxycephalosporanate (29). A solution of 963 mg (1.98 mmol) of the sulfoxide **25** (mixture of α and β isomers), 32 mL of dry benzene, 24 mL of *N,N*-dimethylacetamide, and 3 drops of methanesulfonic acid were refluxed under a Dean-Stark trap, protected from moisture with a drying tube, for 19 h (temperature of external heating bath was maintained between 110 and 120 °C). Removal of the solvent by distillation under reduced pressure (temperature of bath ~50 °C, 2–3 mm) and chromatography of the dark brown residue on silicic acid using methylene chloride as an eluent gave the thiol ester **29** (659 mg, 71%) as a white solid. Recrystallization from methylene chloride–petroleum ether gave the analytically pure sample as thin, white needles: mp 175.5–176.0 °C; IR ($CHCl_3$) 3005, 1780, 1740, and 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 3 H), 3.13 (d, 1 H, J = 18.0 Hz), 3.53 (d, 1 H, J = 18.0 Hz), 4.70 (d, 1 H, J = 13.0 Hz), 5.03 (d, 1 H, J = 13.0 Hz), 5.10 (d, 1 H, J = 4.0 Hz), 5.64 (d, 1 H, J = 4.0 Hz), 7.1–8.2 (m, 5 H).

Anal. Calcd for $C_{17}H_{14}NO_4Cl_3S_2$: C, 43.74; H, 3.02; N, 3.00; Cl, 22.78; S, 13.74. Found: C, 43.66; H, 3.04; N, 3.01; Cl, 22.73; S, 13.64.

Synthesis of β,β,β-Trichloroethyl 7β-(Phenylacetylthio)deacetoxycephalosporanate (30). In the same manner as described for **29** (pure less polar sulfoxide **26** used) the thiol ester **30** (232 mg, 91%) was isolated as an oil which crystallized on standing. Recrystallization from methylene chloride–petroleum ether gave the analytically pure sample: mp 103.0–104.5 °C; IR ($CHCl_3$) 3005, 1780, and 1730 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.10 (d, 1 H, J = 18.0 Hz), 3.43 (d, 1 H, J = 18.0 Hz), 3.83 (s, 2 H), 4.77 (d, 1 H, J = 12.0 Hz), 4.95 (d, 1 H, J = 12.0 Hz), 4.95 (d, 1 H, J = 4.0 Hz), 5.33 (d, 1 H, J = 4.0 Hz), 7.10 (s, 5 H).

Anal. Calcd for $C_{18}H_{16}NO_4Cl_3S_2$: C, 44.96; H, 3.35; N, 2.91; Cl, 22.12; S, 13.34. Found: C, 44.97; H, 3.38; N, 2.84; Cl, 22.10; S, 13.16.

Synthesis of β,β,β-Trichloroethyl 7β-(Phenoxyacetylthio)-deacetoxycephalosporanate (31). A solution of *m*-chloroperbenzoic acid (357 mg, 2.06 mmol) in 20 mL of chloroform was added dropwise over 30 min to an ice-cold solution of the sulfide **10** (1.025 g, 2.05 mmol) in 50 mL of chloroform. After the addition, the solution was stirred at 0 °C for 3.5 h, washed with aqueous $NaHCO_3$, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residual oil (1.05 g) was dissolved in 32 mL of dry benzene. *N,N*-Dimethylacetamide (24 mL) and 3 drops of methanesulfonic acid were added and the mixture refluxed under a Dean-Stark trap, protected from moisture with a drying tube, for 19 h (temperature of external heating bath maintained at 110–120 °C). Removal of the solvent by distillation (temperature of heating bath 50–60 °C, 2–3 mm) and chromatography of the dark brown residue on silicic acid using methylene chloride as an eluent gave the thiol ester **31** (716 mg, 70%) as a crystalline material. Recrystallization from CH_2Cl_2–petroleum ether gave the analytically pure sample: mp 148.5–149.5 °C; IR ($CHCl_3$) 3005, 1780, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 3 H), 3.17 (d, 1 H, J = 18.0 Hz), 3.53 (d, 1 H, J = 18.0 Hz), 4.70 (s, 2 H), 4.70 (d, 1 H, J = 12.0 Hz), 5.00 (d, 1 H, J = 12.0 Hz), 5.05 (d, 1 H, J = 4.0 Hz), 5.45 (d, 1 H, J = 4.0 Hz), 6.7–7.4 (m, 5 H).

Anal. Calcd for $C_{18}H_{16}NO_5Cl_3S_2$: C, 43.52; H, 3.25; N, 2.82; Cl, 21.41; S, 12.91. Found: C, 43.57; H, 3.58; N, 2.77; Cl, 21.40, S, 12.66.

Synthesis of β,β,β-Trichloroethyl 7β-(Chloroacetylthio)deacetoxycephalosporanate (32). In the same manner as described for **31**, the thiol ester **32** (396 mg, 39%) was isolated as a crystalline material. The product was recrystallized from ether–petroleum ether: mp 134–137 °C; IR ($CHCl_3$) 1780 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.28 (s, 3 H), 3.20 (d, 1 H, J = 17.0 Hz), 3.57 (d, 1 H, J = 17.0 Hz), 4.27 (s, 2 H), 4.77 (d, 1 H, J = 12.0 Hz), 5.00 (d, 1 H, J = 12.0 Hz), 5.10 (d, 1 H, J = 4.0 Hz), 5.46 (d, 1 H, J = 4.0 Hz).

Synthesis of β,β,β-Trichloroethyl 7β-Mercaptodeacetoxycephalosporanate (33). The same manner as described for **21** (starting from either the phenoxyacetyl or chloroacetyl derivatives **31** or **32**) the mercaptan **33** was isolated in 75–80% yield as an oil (in the case of **31** methyl phenoxyacetate had to be removed by chromatography: silicic acid–methylene chloride): IR (neat) 2550, 1770, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.32 (d, 4 H, J = 4.0 Hz, $-CH_3$ and $-SH$), 3.20 (d, 1 H, J = 18.0 Hz), 3.57 (d, 1 H, J = 18.0 Hz), 4.4–5.2 (m, 3 H, $-CH_2CCl_3$ and H-6), 5.01 (d, 1 H, J = 4.0 Hz).

Synthesis of β,β,β-Trichloroethyl 7β-(Thiophene-2-acetylthio)deacetoxycephalosporanate (34). In the same manner as described for **22**, the thiol ester **34** was isolated as an oil (352 mg, 82%) after chromatography on silicic acid using methylene chloride as an eluent: IR ($CHCl_3$) 1780, 1735, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.20 (d, 1 H, J = 18.0 Hz), 3.60 (d, 1 H, J = 18.0 Hz), 4.17 (s, 2 H), 4.83 (d, 1 H, J = 12.0 Hz), 5.07 (d, 1 H, J = 12.0 Hz), 5.13 (d, 1 H, J = 4.0 Hz), 5.57 (d, 1 H, J = 4.0 Hz), 6.8–7.4 (m, 3 H).

Synthesis of β,β,β-Trichloroethyl 7β-(D-α-*tert*-Butoxycarboxamidophenylacetylthio)deacetoxycephalosporanate (35). In the same manner as described for **22**, the thiol ester **35** was isolated as an oil (316 mg, 82%) after chromatography on silicic acid using 1% ether–methylene chloride (v/v) as an eluent: IR (neat) 3350, 1780, and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 9 H), 2.23 (s, 3 H), 3.15 (d, 1 H, J = 18.0 Hz), 3.43 (d, 1 H, J = 18.0 Hz), 4.73 (d, 1 H, J = 12.0 Hz), 5.00 (d, 1 H, J = 12.0 Hz), 5.03 (d, 1 H, J = 4.0 Hz), 5.2–5.5 (m, 3 H), 7.25 (s, 5 H).

Synthesis of β,β,β-Trichloroethyl 7-Hydrazonopenicillanate (5). A solution of 3.04 g (8.5 mmol) of the diazo ester **3** in 250 mL of THF was saturated with H_2S and then stirred (stoppered) at room temperature overnight. After removal of the solvent (no heat) under reduced pressure, a yellowish-white solid remained. Trituration with ether gave the hydrazone **5** (2.02 g, 66%) as a white solid: mp 167–168 °C dec; IR ($CHCl_3$) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.67 (s, 3 H), 4.53 (s, 1 H), 4.67 (s, 2 H), 5.60 (s, 1 H), 5.7–6.2 (m, 2 H).

Anal. Calcd for $C_{10}H_{12}N_3O_3Cl_3S$: C, 33.30; H, 3.35; N, 11.65; Cl, 29.49; S, 8.98. Found: C, 33.34; H, 3.52; N, 11.61; Cl, 29.60; S, 8.72.

General Procedure for the Removal of the Protective Group. The ester (100–200 mg) was dissolved in 90% HOAc (1–2 mL of DMF was added if ester did not dissolve) and the solution cooled to 0 °C before 1–1.5 g of zinc dust was added. The mixture was stirred at 0 °C for 3–5 h. Removal of the zinc by filtration through Celite into a flask containing 100 mL of ice water and washing of the zinc with methylene chloride (50 mL) yielded a two-phase system. Separation of the organic layer, extraction of the aqueous layer with several methylene chloride–zinc washings, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat) afforded the free acid. For purification (if required) the acid was dissolved in methylene chloride and extracted with aqueous $NaHCO_3$. The aqueous layer, after being extracted several times with methylene chloride, was cooled with ice and acidified with dilute HCl. Extraction with methylene chloride, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat) gave the pure acid.

For **23** and **35** after removal of the trichloroethyl group as described above, the acid was dissolved in 1 mL of anisole and the solution cooled to 0 °C before 7 mL of trifluoroacetic acid (previously cooled to 0 °C) was added. After stirring at 0 °C for 1 h, the solvent was removed under reduced pressure (2–3 mm keeping the solution at 0 °C during the process). Freeze drying of the residual oil from benzene afforded the acids as solid compounds which were bioassayed without purification.

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