action mixture was heated at reflux for 5.5 h while maintaining the N_2 atmosphere and then poured into 1.5 L of ice water containing 10 g of ascorbic acid. When the blue color of the aqueous phase disappeared, the organic phase was separated and the voltatiles were removed under reduced pressure (1 mm) with warming (80 °C) leaving 503 g of unreacted ferrocene and trifluoroacetylated ferrocene derivatives. This residue was hydrolyzed by stirring and heating to boiling in 1 L of CH_3OH containing 40 g (0.71 mol) of KOH. The resulting mixture was poured into 3 L of ice water and allowed to stand several hours to permit crystallization of products. The solids were separated by filtration and dried on the filter by sucking air through to leave 437 g (theoretical amount is 440 g) of products and unreacted ferrocene. This was extracted with five 3-L portions of boiling CH_2Cl_2 leaving 2.2 g of undissolved yellow powder (impure **9**).

The reaction mixture was separated by chromatography. The five 3-L portions of extract were poured onto an 85 × 440 mm alumina column, activity III (column packed in CH_2Cl_2), in the order in which they were taken. All unreacted ferrocene had been eluted by the time the last 3-L portion had been added. Evaporation of CH_2Cl_2 from this eluate left 298 g (1.60 mol) of ferrocene. There remained four well-defined bands on the column. The two bottom bands were eluted with CH_2Cl_2. The material from the first one, 0.7 g, was not identified. The next band, 4.0 g (0.013 mol, 4.1% yield), was identified by NMR as **5**.

The third (major) band was eluted with 4 L of 1% CH_3OH in CH_2Cl_2, 2 L of 2% CH_3OH in CH_2Cl_2, and then 6 L of 4% CH_3OH in CH_2Cl_2. (Starting elution with 4% CH_3OH in CH_2Cl_2 may cause 4,4-diferrocenylheptane-1,7-diol (**3**) to crystallize in the alumina column.) Evaporation of solvent left 114 g of a mixture of **6** and **3**. This mixture was dissolved in 1.8 L of boiling CH_2ClCH_2Cl, filtered, concentrated to 600 mL, and cooled to give 101.3 g (0.202 mol, 65% yield) of **3**, mp 168–171 °C. [Solubility of **3** is 0.38 g/100 mL of CH_2CCH_2Cl at 25 °C, indicating the presence of an additional 2.5 g of **3** in the mother liquor for a total of 103.8 g (0.207 mol, 67% yield) of **3**.] The presence of **6** and **3** in the mother liquor was shown by thin-layer chromatography on SiO_2 plates. A sample of **3** was recrystallized from CH_3OH, mp 169–171 °C.

Anal. Calcd for $C_{27}H_{32}Fe_2O_2$: C, 64.82; H, 6.45; Fe, 22.33; mol wt, 500. Found: C, 64.65; H, 6.50; Fe, 22.24; *m/e* 500.

After removal of the major band the alumina column was treated with 2 L of 6% CH_3OH in CH_2Cl_2 and 2 L of 10% CH_3OH in CH_2Cl_2. This developed the remaining band into two bands and eluted one to give 2.0 g of material which was not identified. The remaining band was removed with 25% CH_3OH in CH_2Cl_2. Evaporation of solvent left 10.4 g of material which was combined with the 2.2 g of undissolved yellow powder left after the initial extraction with CH_2Cl_2. This was dissolved in 4 L of hot CH_3OH, filtered, concentrated to 500 mL, and cooled to give 7.5 g (0.0092 mol, 5.9% yield) of **9**, mp 202–205 °C. [Solubility of **9** is 0.19 g/100 mL of CH_3OH at 25 °C, indicating the presence of an additional 0.95 g of **9** in the mother liquor for a total of 8.5 g (0.0104 mol, 6.7% yield) of **9**.] Another recrystallization from CH_3OH raised the melting point to 203–205 °C.

Anal. Calcd for $C_{44}H_{54}Fe_3O_4$: C, 64.89; H, 6.68; Fe, 20.57. Found: C, 64.87; H, 6.70; Fe, 20.11.

Acknowledgment. Appreciation is expressed to Donald W. Moore of this Laboratory for NMR spectra and their interpretation.

Registry No.—**4**, 176-25-0; ferrocene, 102-54-5.

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Reaction of 6(7)-Diazopenicillanates and Diazocephalosporanates with Sulfenyl Chlorides. Preparation of 6(7)α-Methoxy-Substituted Thiol Penicillanates and Thiol Cephalosporanates

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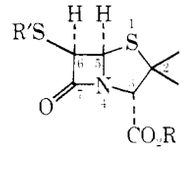
Reaction of diazo esters **3**, **10**, and **16** with sulfenyl chlorides in the presence of methanol gave 6(7)-α-methoxy thiol penicillanates and thiol cephalosporanates. Reaction of **10** and **16** with β,β,β-trichloroethoxycarbonylsulfenyl chloride in the presence of methanol gave the esters **12** and **19** which when treated with Zn–90% HOAc at 0 °C gave the mercaptans **13** and **20**. Mercaptans **13** and **20** were acylated by standard procedures.

A method has been developed in this laboratory for the preparation of sulfur analogues of penicillins and deacetoxycephalosporins of the general structures **1** and **2** where R′ can be either an alkyl group or an acyl group.[1] The isolation of cephalosporin derivatives from species of *Streptomyces* containing an α-methoxy group in the 7 position which exhibited greater activity than cephalosporin C against gram-negative organisms[2] suggested that the sulfur analogues **1** and **2** might also show increased activity with the introduction of an α-methoxy group in the 6(7) position. We wish to report here the preparation of such derivatives by reaction of the diazo esters **3**, **10**, and **16** with sulfenyl chlorides in the presence of methanol.



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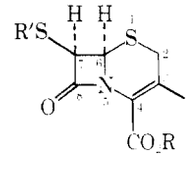

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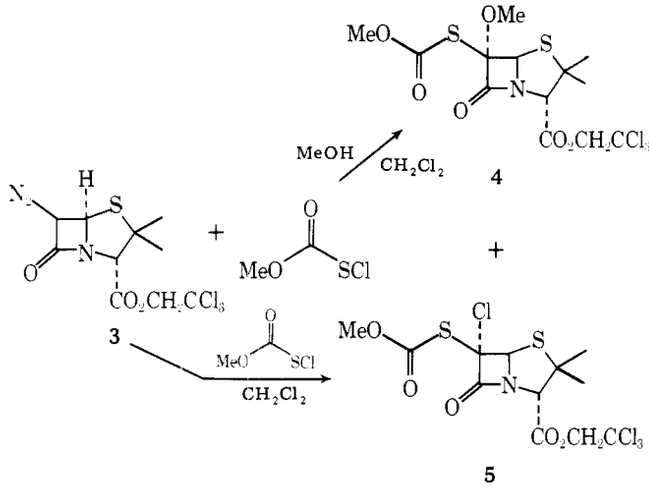
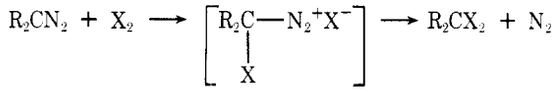
Scheme I



Results and Discussion

Treatment of the diazo ester **3** with carbomethoxysulfenyl chloride in methylene chloride containing an excess of methanol gave, after chromatography on silicic acid, the 6α-methoxy ester **4** in 78% yield along with a small amount (3%) of the 6α-chloro ester **5**. The 6α-chloro ester **5** was obtained in 88% yield by reaction of **3** with the sulfenyl chloride in the absence of methanol[3] (Scheme I).

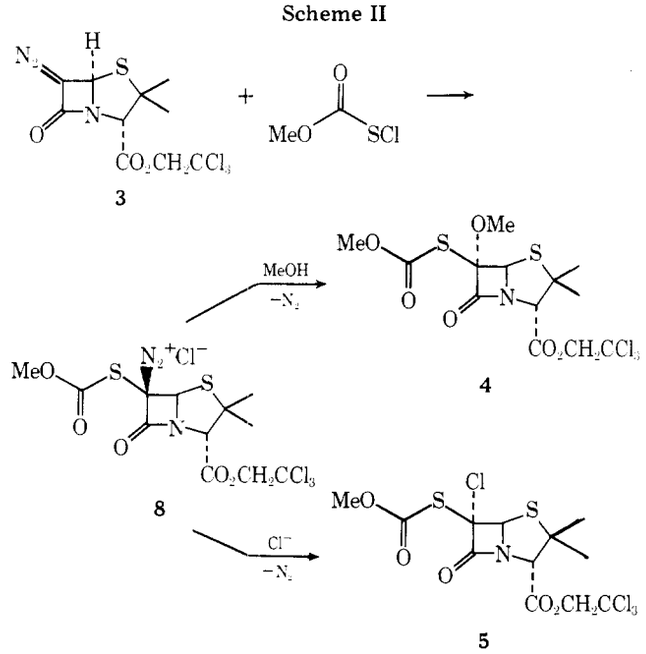
The stereochemistry at C-6 in **4** and **5** has been assigned from mechanistic considerations. Diazo compounds react readily with halogens giving geminal dihalides, the reaction proceeding through the diazonium intermediate shown below.[4] Reaction of **3** with the sulfur of the sulfenyl chloride



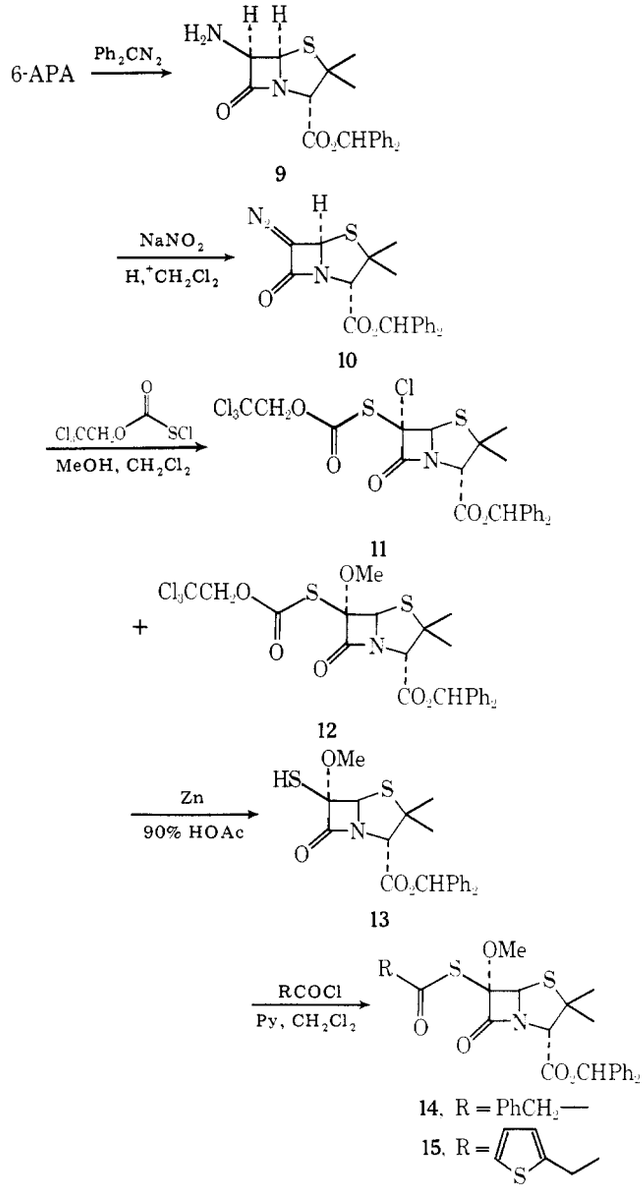
will initially give the diazonium intermediate **8**,[5] presumably with the stereochemistry indicated (see ref 6). Addition of methanol from the least hindered α face of the β-lactam ring[6] will give the 6α-methoxy ester **4** whereas addition of chloride ion will give **5**[7] (Scheme II).

Esterification of 6-APA with diphenyldiazomethane gave the benzhydryl amine **9** which was converted to the diazo ester

Scheme II



Scheme III

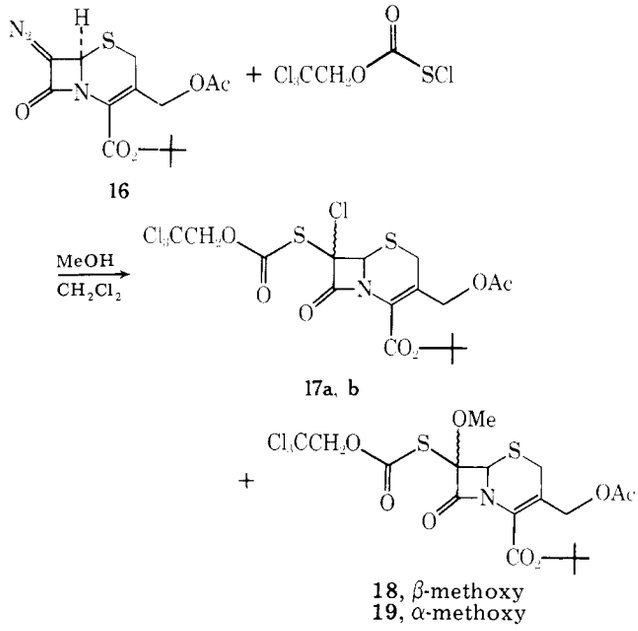


10 by treatment with sodium nitrite in 1 N $HClO_4$ and methylene chloride.[8] Reaction of **10** with β,β,β-trichloroethoxycarbonylsulfenyl chloride and an excess of methanol gave, after chromatography on silica gel,[9] the 6α-chloro ester **11** (1%) and the 6α-methoxy ester **12**[10] (70%). Removal of the trichloroethyl group from **12** with Zn–90% HOAc at 0 °C gave the mercaptan **13** in quantitative yield as a crystalline product. Acylation of **13** with phenylacetyl chloride and thiophene-2-acetyl chloride in methylene chloride containing an equivalent of pyridine gave the thiol esters **14** (77%) and **15** (83%), respectively (Scheme III).

In the cephalosporin series the mercaptan **20** was made by the same sequence of reactions used in the penicillin series. Reaction of the diazo ester **16** with β,β,β-trichloroethoxycarbonylsulfenyl chloride gave, after chromatography on silica gel (see ref 9), the 7α and β-chloro esters **17a** and **17b** as a mixture (oil) in 1% yield[11] and the 7β and α-methoxy esters **18** and **19** as crystalline products in 7% and 35% yields, respectively[12] (Scheme IV).

The assignment of the stereochemistry at C-7 in **19**, the major product in the reaction, is analogous to that given in the penicillin series. The fact that **18** and both epimers of **17** (in a ratio of approximately 2:1 by NMR integration of the C-6 proton in the crude reaction mixture) were isolated in rea-

Scheme IV



sonable quantities is presumably due to the fact that the dihydrothiazine ring does not shield the β face of the β-lactam ring to the same extent that the thiazolidine ring does in the penicillin series (vide supra).

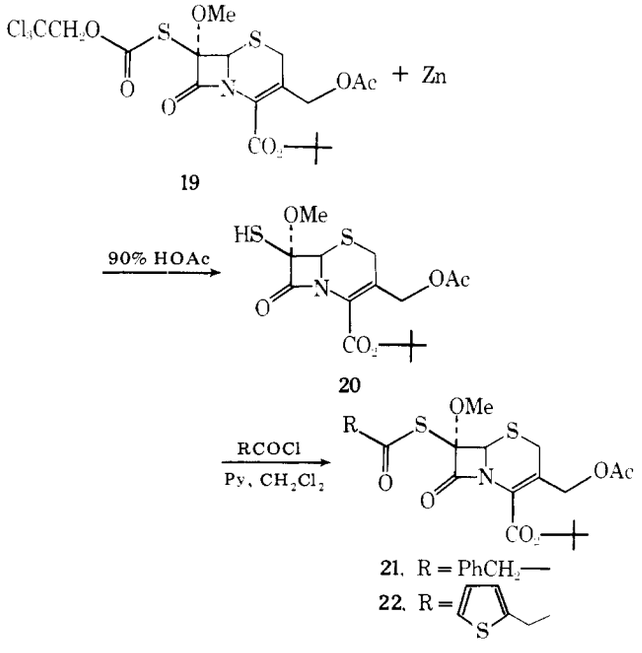
Removal of the trichloroethyl group from **19** in the same manner as described for **12** gave the mercaptan **20** as an unstable oil in quantitative yield. Acylation of **20** with phenylacetyl chloride and thiophene-2-acetyl chloride gave the corresponding esters **21** and **22** in 59% and 68% yields, respectively (Scheme V).

After removal of the protective groups[13] (see Experimental Section), the free acids were tested in vitro for bioactivity. Minimum inhibitory concentration (MIC) values are in micrograms per milliliter. Only the acids from **21** and **22** showed appreciable activity against the microorganisms used. Their values against *Bacillus subtilis* ATCC 6051 were <6.25 and 50, respectively.

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 spectrometer 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. High resolution mass spectra were recorded on a CEC-110B high-resolution Mattauch-Herzog mass spectrometer. Microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Routine thin-layer chromatography was run on Baker-flex silica gel 1B-F TLC sheets. Preparative thick-layer chromatography was performed on EM Reagents precoated silica gel 60 F-254 plates (2 mm thickness). Column chromatography was performed with either Mallinckrodt silicic acid (100 mesh) or EM Reagents silica gel 60 (finer than 230 mesh).

Scheme V



β,β,β-Trichloroethyl 6-diazopenicillanate (3),[14] chlorocarbonylsulfenyl chloride,[15] carbomethoxysulfenyl chloride,[16] 7-diazocephalosporanic acid *tert*-butyl ester,[17] and thiophene-2-acetyl chloride[18] were prepared by literature procedures.

Synthesis of β,β,β-Trichloroethyl 6β-(Methoxycarbothiol)-6-chloropenicillanate (5). Carbomethoxysulfenyl chloride[16] (768.8 mg, 6.08 mmol) was added to an ice-cold solution of 2.1729 g (6.06 mmol) of the diazo ester **3**[14] in 50 mL of methylene chloride. There was an immediate evolution of gas. The solution was stirred at 0 °C for 30 min and then the solvent removed under reduced pressure. The residual oil was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave the chloro ester **5** (2.44 g, 88% as an oil; one spot on TLC): IR (CH_2Cl_2) 2960, 1790, 1765 sh, and 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.63 (s, 3 H), 3.93 (s, 3 H), 4.68 (s, 1 H), 4.83 (s, 2 H), 5.87 (s, 1 H); MS *m/e* 454.9000 (M^+, calcd for $C_{12}H_{13}NO_5Cl_4S_2$, 454.8990).

Isolation of a slower moving fraction gave 43.2 mg of an oil which was one spot by TLC; however, its NMR suggested the presence of more than one component. One of the components is identical (by NMR) with the product isolated in the preparation of **4** and believed to be the 6β-chloro ester **6** (see ref 3 and the next experimental procedure).

Synthesis of β,β,β-Trichloroethyl 6β-(Methoxycarbothio)-6-methoxypenicillanate (4). Carbomethoxysulfenyl chloride (1.0803 g, 8.54 mmol) was added to an ice-cold solution of the diazo ester **3** (3.0050 g, 8.38 mmol) in 50 mL of methylene chloride and 50 mL of methanol. There was an immediate evolution of gas. The solution was stirred at 0 °C for 30 min and the solvent removed under reduced pressure. The residual oil was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave the chloro ester **5** as an oil (132.1 mg, 3%) identical in all respects (NMR, IR, and TLC) with that obtained by treatment of the diazo ester **3** with carbomethoxysulfenyl chloride in the absence of methanol.

Isolation of a slower moving fraction gave 28.7 mg of an oil which was subjected to further chromatography on two 20 × 20 mm silica gel plates using methylene chloride–carbon tetrachloride as eluents. Isolation of the most polar fraction gave 18.9 mg (0.5%) of an oil whose spectral data are in complete agreement with the 6β-chloro ester **6**: IR (CH_2Cl_2) 2950, 1790, and 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.83 (s, 3 H), 3.92 (s, 3 H), 4.65 (s, 1 H), 4.78 (s, 2 H), 5.70 (s, 1 H); MS *m/e* 395.8868 ($M^+ - 59$, calcd for $C_{10}H_{10}NO_3Cl_4S_2$, 395.8856).

Isolation of the slowest moving fraction gave 2.97 g (78%) of the 6α-methoxy ester **4** as an oil (one spot on TLC): IR (CH_2Cl_2) 2950, 1775, 1755 sh, and 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.65 (s, 3 H), 3.68 (s, 3 H), 3.88 (s, 3 H), 4.63 (s, 1 H), 4.83 (s, 2 H), 5.68 (s, 1 H); MS *m/e* 450.9504 (M^+, calcd for $C_{13}H_{16}NO_6Cl_3S_2$, 450.9485).

Synthesis of Benzhydryl 6-Aminopenicillanate (9). A mixture of 5.400 g (25.0 mmol) of 6-APA and 4.850 g (25.0 mmol) of diphenyldiazomethane in 75 mL of methylene chloride and 25 mL of methanol was stirred at room temperature for 44 h. After approximately 24 h and 30 h, additional 1-g portions of diphenyldiazomethane were added. The solid was removed by filtration and the filtrate extracted with ice-cold dilute HCl. An emulsion formed which required more than 3 h to separate (during this time the mixture warmed to room temperature). The organic layer was separated and the aqueous layer extracted twice with methylene chloride (emulsions). The aqueous layer was partitioned with methylene chloride and made basic with $NaHCO_3$. After extraction with methylene chloride, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat), the benzhydryl ester (2.99 g, 31%) was isolated as an oil: IR (CH_2Cl_2) 3380, 3050, 2960, 1775, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.60 (s, 3 H), 1.80 (s, 2 H), 4.40 (d, 1 H, J = 4.0 Hz), 4.47 (s, 1 H), 5.37 (d, 1 H, J = 4.0 Hz), 6.82 (s, 1 H), 7.20 (s, 10 H).

Synthesis of Benzhydryl 6-Diazopenicillanate (10). Ice water (100 mL), sodium nitrite (232.5 mg, 3.37 mmol), and 3 mL of 1 N $HClO_4$ were added (in that order) to an ice-cold solution of the amine

in 100 mL of methylene chloride and the mixture was vigorously stirred (mechanical stirrer) at 0 °C for 2 h. The organic layer was separated, washed with cold saturated NaCl, and dried (Na_2SO_4). Removal of the solvent under reduced pressure (no heat) gave a yellow oil which was dissolved in ether–petroleum ether and after standing at approximately −15 °C overnight, the product crystallized (420 mg, 75%). Recrystallization from ether–petroleum ether gave an analytically pure sample: mp 93.0–94.0; IR (CH_2Cl_2) 2090, 1760, and 1700 sh; NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.65 (s, 3 H), 4.47 (s, 1 H), 6.12 (s, 1 H), 6.88 (s, 1 H), 7.30 (s, 10 H).

Anal. Calcd for $C_{21}H_{19}N_3O_3S$: C, 64.10; H, 4.87; N, 10.68; S, 8.15. Found: C, 64.11; H, 4.90; N, 10.52; S, 8.06.

Synthesis of β,β,β-Trichloroethoxycarbonylsulfenyl Chloride. Chlorocarbonylsulfenyl chloride[15] (43.5 mL, 0.52 mol) was added dropwise over 30 min to an ice-cold solution of 50 mL (0.52 mol) of β,β,β-trichloroethanol and 42 mL (0.52 mol) of pyridine in 300 mL of methylene chloride. After the addition, the mixture was stirred at 0 °C for 1.5 h and at room temperature for 1.5 h. The mixture was washed with ice water and ice-cold saturated NaCl. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure.

After removal of the solvent, an oily crystalline material remained (crystalline material believed to be $[Cl_3CCH_2OCOS]_2$). The crystalline material was removed by crystallization from a minimum amount of ether. This process was repeated until as much crystalline material as possible was removed. The remaining yellow liquid was distilled under reduced pressure: fraction collected 54–59 °C (0.25 mm; external bath temperature, 80–90 °C); NMR ($CDCl_3$) δ 5.0 (singlet).

Synthesis of Benzhydryl 6β-(β,β,β-Trichloroethoxycarbothio)-6-chloropenicillanate (11). The diazo ester **10** was prepared as described above. After removal of the Na_2SO_4 by filtration, the methylene chloride solution of **10** was cooled to 0 °C and used in the following reaction.

β,β,β-Trichloroethoxycarbonylsulfenyl chloride (243.8 mg, 5.00 mmol; 1 equiv based on starting benzhydryl amine) was added to the above ice-cold solution of **10**. The solution was stirred at 0 °C for approximately 30 min and then the solvent was removed under reduced pressure. The residual oil was chromatographed on silica gel 60 (>230 mesh) using methylene chloride as an eluent. Isolation of the major fraction gave the 6α-chloro ester **11** (593 mg, 20%; oil) as the only identifiable β-lactam component: IR (CH_2Cl_2) 3040, 2950, 1790, and 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.60 (s, 3 H), 4.58 (s, 1 H), 4.73 (d, 1 H, J = 10.0 Hz), 4.93 (d, 1 H, J = 10.0 Hz), 5.80 (s, 1 H), 6.83 (s, 1 H), 7.23 (s, 10 H).

Synthesis of Benzhydryl 6β-(β,β,β-Trichloroethoxycarbothio)-6-methoxypenicillinate (12). The diazo ester **10** (starting with 2.8364 g, 7.43 mmol of benzhydryl amine **9** in 150 mL of methylene chloride) was prepared as described above. After removal of the Na_2SO_4 by filtration, the solution was cooled to 0 °C and 150 mL of methanol added.

β,β,β-Trichloroethoxycarbonylsulfenyl chloride (1.800 g, 7.38 mmol) was added to the above ice-cold solution. After stirring at 0 °C for 15 min and removal of the solvent under reduced pressure, the residual oil was chromatographed on silica gel 60 (>230 mesh) using methylene chloride as an eluent. Isolation of a minor fraction gave the 6α-chloro ester **11** (54 mg, 1%) identical in all respects (IR, NMR, and TLC) with that obtained from the reaction of **10** with β,β,β-trichloroethoxycarbonylsulfenyl chloride in the absence of methanol.

Isolation of the major fraction gave the 6α-methoxy ester **12** (3.16 g, 70%) as an oil (1 spot on TLC) as the only other β-lactam component: IR (CH_2Cl_2) 1775 and 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.60 (s, 3 H), 3.68 (s, 3 H), 4.60 (s, 1 H), 4.85 (s, 2 H), 5.70 (s, 1 H), 6.92 (s, 1 H), 7.33 (s, 10 H); MS m/e 603.0130 (M^+, calcd for $C_{25}H_{24}NO_6Cl_3S_2$, 603.0111).

Synthesis of Benzhydryl 6β-Mercapto-6-methoxypenicillanate (13). The 6α-methoxy ester **12** (1.2346 g, 2.04 mmol) was dissolved in 30 mL of 90% HOAc and the solution cooled to 0 °C before 1.6 g of zinc dust was added. The mixture was stirred at 0 °C for 5 h. Removal of the zinc by filtration through celite into a flask containing ice water and washing of the zinc with methylene chloride gave a two-phase system. The aqueous layer was made basic with $NaHCO_3$ and extracted with the organic layer. 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) gave the mercaptan **13** as a crystalline product in quantitative yield. Recrystallization from methylene chloride–petroleum ether gave an analytically pure sample: mp 127.5–129.0 °C; IR (CH_2Cl_2) 3030, 2950, 1775, and 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.67 (s, 3 H), 2.55 (s, 1 H), 3.50 (s, 3 H), 4.55 (s, 1 H), 5.40 (s, 1 H), 6.85 (s, 1 H), 7.25 (s, 10 H).

Anal. Calcd for $C_{22}H_{23}NO_4S_2$: C, 61.52; H, 5.40; N, 3.26; S, 14.93. Found: C, 61.58; H, 5.41; N, 3.23; S, 14.93.

Synthesis of Benzhydryl 6β-(Phenylacetylthio)-6-methoxypenicillanate (14). A solution of 397.8 mg (9.26 mmol) of the mercaptan **13** in 20 mL of methylene chloride was cooled to 0 °C before 122 μL (9.22 mmol) of phenylacetyl chloride and 75 μL (9.27 mmol) of pyridine were added. The solution was stirred at 0 °C for 3 h and then extracted with ice-cold dilute HCl and aqueous $NaHCO_3$ and dried ($MgSO_4$), and the solvent removed under reduced pressure. After chromatography on silica gel 60 (>230 mesh) using methylene chloride as an eluent, the 6α-methoxy ester **14** (389 mg, 77%) was isolated as an oil: IR (CH_2Cl_2) 3050, 2925, 1770, 1740, and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.45 (s, 3 H), 3.50 (s, 3 H), 3.78 (s, 2 H), 4.45 (s, 1 H), 5.63 (s, 1 H), 6.77 (s, 1 H), 6.9–7.3 (m, 15 H).

Synthesis of Benzhydryl 6β-(Thiophene-2-acetylthio)-6-methoxypenicillanate (15). In the same manner as described for the preparation of **14**, the 6α-methoxy ester **15** was isolated as an oil (83%) after chromatography on silica gel 60 (>230 mesh) using methylene chloride as an eluent: IR (CH_2Cl_2) 3050, 2960, 1775, 1740, and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.48 (s, 3 H), 3.53 (s, 3 H), 3.98 (s, 2 H), 4.48 (s, 1 H), 5.70 (s, 1 H), 6.7–7.5 (m, 14 H).

7-Aminocephalosporanic acid *tert*-butyl ester was prepared according to the literature[19] and purified in the following manner. After removal of the solvent under reduced pressure (no heat), the crude product (dark brown) was dissolved in methylene chloride and extracted with ice-cold dilute HCl. The aqueous layer (kept cold) was extracted with methylene chloride (twice), partitioned with methylene chloride, and made basic with $NaHCO_3$. After separation of the organic layer, repeated extraction of the aqueous layer with methylene chloride (four times), drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat), the product was isolated as a light yellow crystalline material. Recrystallization from methylene chloride (minimum amount)–ether–petroleum ether gave 7-aminocephalosporanic acid *tert*-butyl ester as a white crystalline product. The yield of the diazo ester **16** depends on the purity of this starting material.

Synthesis of *tert*-Butyl 7-(β,β,β-Trichloroethoxycarbothio)-7-chlorocephalosporanates (17a and 17b). A vigorously stirred (mechanical stirrer) solution of *tert*-butyl 7-aminocephalosporinate (2.000 g, 6.10 mmol) in 200 mL of methylene chloride was cooled to 0 °C before 200 mL of ice water, 18.000 g (0.261 mmol) of sodium nitrite, and 1.150 g (6.04 mmol) of p-TsOH·H_2O were added in that order. After 5 min, a total of 1.660 g (8.73 mmol) of p-TsOH·H_2O was added gradually over 40 min. After the last addition, the mixture was stirred at 0 °C for 15 min and then the organic layer separated (kept cold), washed with cold saturated NaCl, and dried (Na_2SO_4). The Na_2SO_4 was removed by filtration and the filtrate cooled to 0 °C before the addition of 1.20 g (4.92 mmol; 0.8 equiv based on starting amine) of β,β,β-trichloroethoxycarbonylsulfenyl chloride. The solution was stirred at 0 °C for 15 min and then the solvent removed under reduced pressure and the residual oil chromatographed on silica gel 60 (>230 mesh) using 100:1 methylene chloride/ether (v/v) as an eluent. The chloro esters **17a** and **17b** (365 mg of oil, 11%) were isolated as a mixture of epimers in a ratio of approximately 2:1 by NMR integration of the C-6 protons: IR (CH_2Cl_2) 2950, 1790, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 18 H), 2.15 (s, 6 H), 3.3–3.7 (m, 4 H), 4.7–5.4 (m, 10 H; C-6 protons are singlets at 5.17 and 5.27 in a ratio of 1:2, respectively).

The mixture of **17a** and **17b** (254 mg) was chromatographed on 100 g of silica gel 60 (>230 mesh; dried at 125 °C for 12 h prior to use) using 200:1 methylene chloride/ether (v/v) as an eluent. Fractions collected were monitored by NMR analysis. Three fractions were collected. The middle fraction was a mixture of epimers.

Less polar fraction (20 mg of oil): IR (CH_2Cl_2) 2925, 1790, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 9 H), 2.10 (s, 3 H), 3.2–3.6 (m, 2 H), 4.5–5.3 (m, 5 H, C-6 proton singlet at 5.17).

More polar isomer (32 mg of oil): IR (CH_2Cl_2) 2950, 1790, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 9 H), 2.12 (s, 3 H), 3.22 (d, 1 H, J = 18.0 Hz), 3.55 (d, 1 H, J = 18.0 Hz), 4.6–5.4 (m, 5 H; C-6 proton singlet at 5.27).

Synthesis of *tert*-Butyl 7-(β,β,β-Trichloroethoxycarbothio)-7-methoxycephalosporanates (18 and 19). A vigorously stirred (mechanical stirrer) solution of *tert*-butyl 7-aminocephalosporanate (2.000 g, 6.10 mmol) in 200 mL of methylene chloride was cooled to 0 °C before 200 mL of ice water, 18.000 g (.261 mmol) of sodium nitrite, and 1.150 g (6.04 mmol) of p-TsOH·H_2O were added in that order. After 5 min a total of 1.660 g (8.73 mmol) of p-TsOH was added gradually over 40 min. After the last addition, the mixture was stirred at 0 °C for 10 min and then the organic layer separated (kept cold), washed with cold saturated NaCl, and dried (Na_2SO_4). The Na_2SO_4

was removed by filtration and the filtrate (approximately 400 mL) cooled to 0 °C before 100 mL of methanol and 1.20 g (4.92 mmol; 0.8 equiv based on starting amine) of β,β,β-trichloroethoxycarbonylsulfenyl chloride were added in that order. The solution was stirred at 0 °C for 30 min and then the solvent removed under reduced pressure. The residual oil was chromatographed on silica gel 60 (>230 mesh) using 100:1 methylene chloride/ether (v/v) as an eluent. Isolation of the least polar β-lactam fraction gave the α and β-chloro esters **17a** and **17b** as a mixture (43 mg of oil, 1%) identical in all respects (IR, NMR and TLC) with the mixture obtained by treatment of the diazo ester **16** with β,β,β-trichloroethoxycarbonylsulfenyl chloride in the absence of methanol.

Isolation of a slower moving fraction gave the 7β-methoxy ester **18** as an oil which crystallized on standing (232 mg, 7%). Recrystallization from methylene chloride–petroleum ether gave an analytically pure sample: mp 95–97 °C; IR (CH_2Cl_2) 2970, 1780, and 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 9 H), 2.15 (s, 3 H), 3.32 (d, 1 H, J = 18.0 Hz), 3.63 (d, 1 H, J = 18.0 Hz), 3.72 (s, 3 H), 4.7–5.3 (m, 5 H; C-6 proton singlet at 5.15).

Anal. Calcd for $C_{18}H_{22}NO_8S_2Cl_3$: C, 39.25; H, 4.03; N, 2.54; Cl, 19.31; S, 11.64. Found: C, 39.19; H, 4.11; N, 2.48; Cl, 19.29; S, 11.85.

Isolation of the slowest moving fraction gave the 7α-methoxy ester **19** as an oil which crystallized on standing (1.18 g, 35%). Recrystallization from methylene chloride–petroleum ether gave an analytically pure sample: mp 85.0–87.5 °C; IR (CH_2Cl_2) 2950, 1775, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 9 H), 2.10 (s, 3 H), 3.25 (d, 1 H, J = 18.0 Hz), 3.62 (d, 1 H, J = 18.0 Hz), 3.73 (s, 3 H), 4.6–5.3 (m, 5 H; C-6 proton singlet at 5.10).

Anal. Calcd for $C_{18}H_{22}NO_8S_2Cl_3$: C, 39.25; H, 4.03; N, 2.54; Cl, 19.31; S, 11.64. Found: C, 39.41; H, 4.16; N, 2.45; Cl, 19.44; S, 11.76.

Synthesis of *tert*-Butyl 7β-Mercapto-7-methoxycephalosporanate (20). In the same manner as described for the preparation of **13**, the mercaptan **20** was isolated as an unstable oil in quantitative yield: IR (CH_2Cl_2) 2950. 2920, 1775, and 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 9 H), 2.10 (s, 3 H), 2.55 (s, 1 H), 3.30 (d, 1 H, J = 18.0 Hz), 3.57 (d, 1 H, J = 18.0 Hz), 3.60 (s, 3 H), 4.80 (d, 1 H, 13.0 Hz), 4.88 (s, 1 H), 5.13 (d, 1 H, J = 13.0 Hz).

Synthesis of *tert*-Butyl 7β-Mercapto-7-methoxycephalosporanate (20). In the same manner as described for the preparation mercaptan **20** was isolated as an oil and used immediately in the following reaction.

A solution of 239 mg (0.64 mmol) of the mercaptan in 10 mL of methylene chloride was cooled to 0 °C before 52 μL (0.64 mmol) of pyridine and 84 μL (0.64 mmol) of phenylacetyl chloride were added in that order. The solution was stirred at 0 °C for 2.75 h and then extracted with ice-cold dilute HCl, aqueous $NaHCO_3$, and dried ($MgSO_4$), and the solvent removed under reduced pressure. After chromatography on silica gel 60 (>230 mesh) using 50:1 methylene chloride/ether (v/v) as an eluent, the 7α-methoxy ester **21** was isolated as an oil (184 mg, 59%) which crystallized on standing. Recrystallization from ether–petroleum ether gave an analytically pure sample: mp 78–80 °C; IR (CH_2Cl_2) 2950, 1775, 1735 sh, and 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.62 (s, 9 H), 2.13 (s, 3 H), 3.20 (d, 1 H, J = 18.0 Hz), 3.60 (d, 1 H, J = 18.0 Hz), 3.62 (s, 3 H), 3.92 (s, 2 H), 4.77 (d, 1 H, J = 14.0 Hz), 5.08 (d, 1 H, J = 14.0 Hz), 5.10 (s, 1 H), 7.30 (s, 5 H).

Anal. Calcd for $C_{23}H_{27}NO_7S_2$: C, 55.97; H, 5.51; N, 2.84; S, 12.99. Found: C, 56.12: H, 5.48; N, 2.78; S, 12.99.

Synthesis of *tert*-Butyl 7β-(Thiophene-2-acetylthio)-7-methoxycephalosporanate (22). In the same manner as described for **21**, the 7α-methoxy ester **22** was isolated as an oil (206 mg, 68%) which crystallized on standing. Recrystallization from ether–petroleum ether gave an analytically pure sample: mp 78–80 °C; IR (CH_2Cl_2) 2950, 1775, 1735 sh, and 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.62 (s, 9 H), 2.10 (s, 3 H), 3.15 (d, 1 H, J = 17.0 Hz), 3.53 (d, 1 H, J = 17.0 Hz), 3.60 (s, 3 H), 3.73 (s, 2 H), 4.70 (d, 1 H, J = 13.0 Hz), 5.00 (d, 1 H, J = 13.0 Hz), 5.03 (s, 1 H), 6.8–7.4 (m, 3 H).

Anal. Calcd for $C_{21}H_{25}NO_7S_3$: C, 50.58; H, 5.03; N, 2.80; S, 19.21. Found: C, 50.62; H, 5.20; N, 2.75; S, 19.31.

General Procedures for Removal of Protective Groups. For removal of the trichloroethyl group from **4**, see ref 1.

For 21 and 22. The esters were dissolved in cold trifluoroacetic acid, and the solution was stirred at 0 °C for 1 h. The TFA was removed by distillation under reduced pressure (2 mm; reaction flask kept in ice bath while TFA was removed) and the residue freeze-dried from benzene. The acids of **21** and **22** were isolated as white solids and bioassayed without purification.

For **12** the benzhydryl group was removed in the same manner as described for the removal of the *tert*-butyl group from **21** and **22**. After freeze drying, the residue was purified in the following manner. 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 partitioned with methylene chloride, 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 of **12**.

For 14 and 15. The esters (70–80 mg) were dissolved in 10 mL of CH_2Cl_2 and the solution was cooled to −77 °C (CO_2–acetone) before the addition of 0.5 mL of trifluoroacetic acid. The solution was warmed to approximately −10 °C (NaCl–H_2O–ice) and stirred at that temperature for 5–6 h. The solution was cooled to −77 °C and 75–100 mL of benzene added. After the contents of the flask solidified, the acids of **14** and **15** were isolated by freeze drying and bioassayed without purification.

In all cases the spectral data were in complete agreement with the structures of the free acids. The NMR spectra showed only signals corresponding to the free acid. Signals corresponding to the protons of the ester protecting group were totally absent, indicating a purity of >95% of the free acid.

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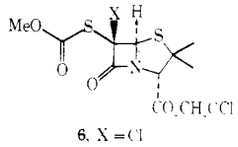
Registry No.—**3,** 51056-24-7; **4,** 65293-10-9; **5,** 65293-11-0; **6,** 65293-12-1; **9,** 47547-28-4; **10,** 65293-13-2; **11,** 65293-14-3; **12,** 65293-15-4; **13,** 65293-16-5; **14,** 65293-17-6; **15,** 65354-55-4; **16,** 58249-92-6; **17a,** 65354-56-5; **17b,** 65293-18-7; **18,** 65293-19-8; **19,** 65293-20-1; **20,** 65293-21-2; **21,** 65293-22-3; **21** acid, 65293-23-4; **22,** 65293-24-5; **22** acid, 65293-25-6; carbomethoxysulfenyl chloride, 26555-40-8; 6-APA, 551-16-6; diphenyldiazomethane, 883-40-9; chlorocarbonylsulfenyl chloride, 2757-23-5; β,β,β-trichloroethanol, 115-20-8; β,β,β-trichloroethoxycarboxylsulfenyl chloride, 65293-26-7; phenylacetyl chloride, 103-80-0; thiophene-2-acetyl chloride, 39098-97-0.

References and Notes

(1) J. C. Sheehan, T. J. Commons, and Y. S. Lo, *J. Org. Chem.*, **42,** 2224 (1977).
(2) E. H. Flynn, "Cephalosporins and Penicillins: Chemistry and Biology", Academic Press, New York, N.Y., 1972, Chapter 15.
(3) In the preparation of **4**, a fraction was isolated which after additional chromatography (see Experimental Section) 18.9 mg (<1%) of an oil was isolated whose spectral data (NMR, IR, and mass spectra) are in complete agreement with the epimeric 6β-chloro ester **6**.



6, X = Cl
7, X = OMe

This component (<1%) was also observed in the preparation of **5**; however, it was not obtained pure. The epimeric 6β-methoxy ester **7** was not isolated in the preparation of **4**. If formed, and very possibly it was, the amount would be small and it could have been lost during the chromatography.
(4) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds", Vol. 2, W. A. Benjamin, Inc., New York, N.Y., 1966, Chapter 10, p 234.
(5) In sulfenyl chlorides of the general structure $RS^+–Cl^-$, the ionized form is as indicated. This is consistent with **3** reacting at sulfur and not chlorine giving **8**. N. Kharasch, "Organic Sulfur Compounds", Vol. 1, Pergamon Press, New York, N.Y., 1961, Chapter 32.
(6) The effect of the thiazolidine ring in penicillins in directing attack to the α face of the β-lactam ring is well known: see ref 1.
(7) There is an instant and rapid evolution of nitrogen upon addition of the sulfenyl chloride to **3**. An analogous mechanistic argument has been presented by B. G. Christensen and co-workers for the formation of a single 6β-bromo-6-methoxypenicillanate when benzyl 6-diazopenicillanate is stirred in MeOH–CH_2Cl_2 containing 1 equiv of NBA: L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Am. Chem. Soc.*, **94,** 1408 (1972).
(8) Although the diazo ester **10** is crystalline and can be obtained analytically pure by recrystallization from ether–petroleum ether, better overall yields are realized if **10** is not isolated (see Experimental Section).
(9) In the case of the benzhydryl penicillanates (and the *tert*-butyl cephalosporanates; vide infra), there is some decomposition during the chromatography. Silica gel was used instead of silicic acid, and a solvent system was chosen such that the products were isolated within 24 h.
(10) The structure of **11** was authenticated by treatment of the diazo ester **10**

with the sulfenyl chloride in the absence of methanol. The epimers (at C-6) of **11** and **12** were not observed. However, if formed it is unlikely they would survive the chromatography: see ref 3 and 9.

(11) The 7-chloro esters **17a** and **17b** were made by treatment of the diazo ester **16** with the sulfenyl chloride in the absence of methanol. After extensive chromatography on silica gel, which decomposed most of the material put on the column (see ref 9), a small amount of each epimer was isolated (see Experimental Section).

(12) The diazo ester **16**, made by the method of Wiering and Wynberg (ref 17), is a crystalline compound; however, again (see ref 8) better overall yields of **19** are obtained if **16** is not isolated. The lower yields in this series compared to the previous two in the penicillin series are attributed mainly to the low yield in the preparation of the diazo ester **16**.

(13) The benzhydryl group has not been used to protect the carboxyl in penicillins because the mild acidic conditions required to remove it destroy the penam system. In the absence of an acylamino group at the C-6 position, which readily reacts with the β-lactam ring to form azlactones, penicillins are more acid stable (see ref 2, p 258). It was therefore anticipated that in the case of the α-methoxy thiol penicillanates, the benzhydryl group could be removed under mild acidic conditions. The carboxyl of **12** was smoothly deprotected with trifluoroacetic acid at 0 °C. With **14** and **15**, these same conditions gave complete destruction of the penam system. However, satisfactory results were obtained when TFA was used with methylene chloride as a solvent (see Experimental Section).

(14) J. C. Sheehan, Y. S. Lo, J. Loliger, and C. Podewell, *J. Org. Chem.*, **39**, 1444 (1974).
(15) German Patent 1 224 720; *Chem. Abstr.*, **65**, 12112h (1966).
(16) G. Zumach and E. Kühle, *Angew. Chem., Int. Ed. Engl.*, **9**, 54 (1970).
(17) J. S. Wiering and H. Wynberg, *J. Org. Chem.*, **41**, 1574 (1976).
(18) U.S. Patent 3 129 224; *Chem. Abstr.*, **61**, 5659e (1964).
(19) E. H. W. Bohme, H. E. Applegate, J. B. Ensing, P. T. Funke, M. S. Puar, and J. E. Dolfini, *J. Org. Chem.*, **38**, 230 (1973).

Computer-Assisted Synthetic Analysis. Performance of Long-Range Strategies for Stereoselective Olefin Synthesis

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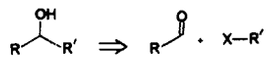
The Harvard program for computer-assisted synthetic analysis (LHASA) has been expanded to include a module which directs antithetic simplifications of olefinic target molecules. The new module employs a readily modifiable data base of C=C transforms (retroreactions) written in chemical English (CHMTRN). Transforms are selected via a unique set-matching process based on prescreen information extracted both from the target molecule and from the transform entries in the data table. Each transform has access to a considerable amount of subgoal power and is thus capable of generating quite long and sophisticated sequences. Several strategies, corresponding to effective plans for polyene synthesis, have been implemented. A number of sample antithetic analyses are included, and future extensions are discussed.

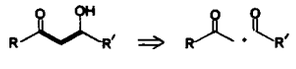
Synthetic methodology for the stereospecific and highly stereoselective construction of carbon–carbon double bonds has expanded dramatically in the last 15 years. Challenges presented by biogenetically interesting isoprenoid molecules, such as squalene[1] and farnesol,[2] and in particular by the insect juvenile hormones,[3] have stimulated development of a large number of versatile techniques for olefin synthesis.[4] To keep pace with these new methods, a special module for olefin synthesis has recently been added to the LHASA[5] computer program. The new package combines stereochemical sophistication[6] with a broad data base of chemical reactions, employing a variety of "strategies" to construct efficient and often elegant routes to polyolefinic molecules.

As previously described,[7] LHASA is an interactive program for synthetic analysis which employs straightforward graphical input and output. The program analyzes an input "target" molecule antithetically, generating a "tree" of potential synthetic precursors. Individual steps in the antithetic analysis correspond to "transforms" (retroreactions) which are chosen, or "keyed," by certain arrangements of functional groups and structural features in the target molecule.

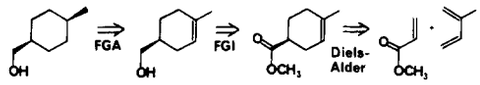
Early work on LHASA divided transforms into two categories, group oriented[8] and substructure oriented.[9] In the former category, an opportunistic, or breadth first, search through the data base selects transforms purely on the basis of arrangements of functionality. A Grignard transform, for instance, is keyed by the presence of a hydroxyl group:



and an Aldol condensation by (among other combinations) a carbonyl group and a hydroxyl separated by a "path" of two bonds:



In the latter category, certain powerful transforms generate antithetic pathways in a depth-first fashion. The existence of an appropriate substructure (for instance a ring of a certain size) is sufficient to key entry into the transform, and the existing functionality is modified as necessary for transform performance:



In this last example, the functionality in the target molecule was not correct for performance of the Diels–Alder disconnection. Accordingly, two nonsimplifying "subgoal" steps, a Functional Group Addition (FGA) of a C=C and a Functional Group Interchange (FGI) of the hydroxyl for the ester group, were performed by the program before the Diels–Alder transform. These steps, like the goal transform, were thoroughly evaluated by the program before display to ensure that they correspond to reasonable synthetic reactions. The subgoal powers of the LHASA program have recently been expanded to include sequential functional group interchange (SEQFGI),[10] double parallel functional group interchange (FGIFGI), and parallel functional group interchange–functional group addition (FGIFGA).

The new package for olefin syntheses combines features of both the group-oriented and substructure-oriented approaches, as described below. Considerable planning preceeded implementation of the module, with six important concepts guiding its development.

First, the data base for the package needed to reflect both the great diversity of new olefin syntheses and the stereochemical specificity of many of these new methods. The efficiency of a simple, functionality based search through all the transforms keyed by the presence of a C=C decreases dramatically with the addition of large numbers of new trans-

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