A Method for the Preparation of 7α-Methoxycephalosporins †

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A method for the preparation of 7α-methoxycephalosporins has been developed. 7β-Phosphoramidodeacetoxycephalosporin (6) and 7β-phosphoramidocephalosporin (14) obtained from the 7β-amino-derivatives (5) and (13), were converted into 7α-methoxy-7β-phosphoramidodeacetoxycephalosporin (7) and 7α-methoxy-7β-phosphoramidocephalosporin (15), respectively, by reaction with LiOMe and Bu^{t}OCl. Treatment of (7) with Bu^{n}Li and Et_3N followed by acylation with phenylacetyl chloride gave 7α-methoxy-7β-phenylketenimino-derivative (11), which were easily hydrated to 7α-methoxy-7β-(phenylacetamido)deacetoxycephalosporin (12). Treatment of (15) under similar conditions afforded, contrary to the result obtained with (7), 7α-methoxy-7β-(phenylacetamido)cephalosporin (16), without any of the corresponding ketenimine. This method was also successfully applied to the synthesis of 6α-methoxypenicillins.

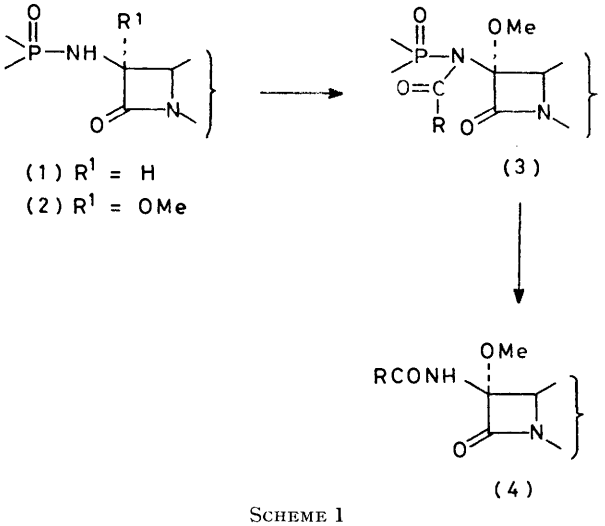
SINCE the discovery of naturally occurring 7α-methoxycephalosporins [1] with enhanced activity, particularly against gram-negative bacteria,[2] many synthetic approaches to these substances have been developed.[3] We report here a method by which cephalosporins can be converted into 7α-methoxycephalosporins *via* the intermediacy of 7α-methoxy-7β-phosphoramidocephalosporins.

RESULTS AND DISCUSSION

Our planned route comprised preparation of the 7α-methoxy-7β-phosphoramidocephalosporins (2) which may be obtained by the application of the well known t-butyl hypochlorite method [3h] to the 7β-phosphoramidocephalosporins (1) and subsequent conversion of (2) with acyl halide (RCOCl) into diacyl dervatives (3), which can be transformed into the desired 7β-acylamino-7α-methoxycephalosporins (4) by selective cleavage of the P–N bond with acid [4] or reduction.[5]

Treatment of t-butyl 7-aminodeacetoxycephalosporanate (5) in methylene chloride with organophosphorus chlorides ‡ such as bis-(2,2,2-trichloroethyl)-phosphorochloridate, dimethyl phosphorochloridate, diphenyl phosphorochloridate, and diphenylphosphinic chloride, in the presence of pyridine gave the corresponding 7β-phosphoramidates,§ (6a) (63%), (6b) (72%), and (6c) (26%), and the 7β-phosphinamide, (6d) (65%). These compounds were converted into the crystalline 7α-methoxy-7β-phosphoramidates,¶ (7a) (93%), (7b) (77%), and (7c) (84%), and the 7α-methoxy-7β-phosphinamide, (7d) (75%), respectively, by reaction with t-butyl hypochlorite and lithium methoxide in tetrahydrofuran at −78 °C (t-butyl hypochlorite method). Similarly, diphenylmethyl 7-aminocephalosporanate (13) was treated with bis-(2,2,2-trichloroethyl)phosphorochloridate to give 7β-phosphoramidate (14) in 51% yield, which was converted into the 7α-methoxy-7β-phosphoramidate (15) by the t-butyl hypochlorite method in 75% yield.

Acylation of the 7α-methoxy-7β-phosphoramidate (7a) with phenylacetyl chloride to give the diacyl derivative (9) was then tried in the presence of strong base. Whereas acylation in the presence of lithium di-isopropylamide or lithium disilazane proved unsuccessful, t-butyl 7α-methoxy-7β-phenylketeniminodeacetoxycephalosporanate (11) ** was obtained unexpectedly in 10—15% yield when the reaction was conducted in the presence of an equimolar amount of sodium hydride (method A) or n-butyl-lithium (method B). The structure of the ketenimine (11) was based on its spectral properties, and its facile conversion with dilute hydrochloric acid into the desired t-butyl 7α-methoxy-7β-phenylacetamidodeacetoxycephalosporanate (12), which was identified by



SCHEME 1

† Part of this paper was presented at the 18th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Georgia, October 1978 (Abstract 150).

‡ Organophosphorus chlorides were obtained commercially or prepared by a known method.[6]

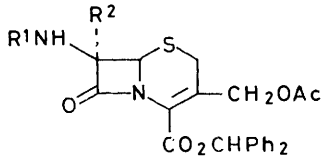
§ The synthesis of 2,2,2-trichloroethyl 7β-dimethylphosphoramidodeacetoxycephalosporanate has been reported *via* the ring expansion of 2,2,2-trichloroethyl 6β-dimethylphosphoramidopenicillanate sulphoxide.[7]

¶ The configuration at C-7 was assigned from steric considerations, and from results already obtained in the introduction of the methoxy-group at C-7 of the cephem ring by the t-butyl hypochlorite method,[3h] together with the fact that subsequent reactions of these compounds gave the known 7β-acylamino-7α-methoxy-compounds (12) and (16).

** After completion of our work (*Japan Patent Application*, July 24, 1975), an alternative synthesis of a similar ketenimine was reported starting from 7-(α-halogeno-substituted)acetamidocephalosporins.[3l]

comparison with an authentic sample.[3c] A possible mechanism for the formation of the ketenimine compound is illustrated in Scheme 2.[8]

Thus the ketenimine formation reaction together with the facile hydration provides a method for the preparation of 7β-acylamino-7α-methoxycephalosporins. Several attempts were then made to improve the yield of (11). Acylation using a two-fold molar excess of n-butyl-lithium to improve the yield was unsuccessful. Monitoring of the reaction by t.l.c., after successive treatment



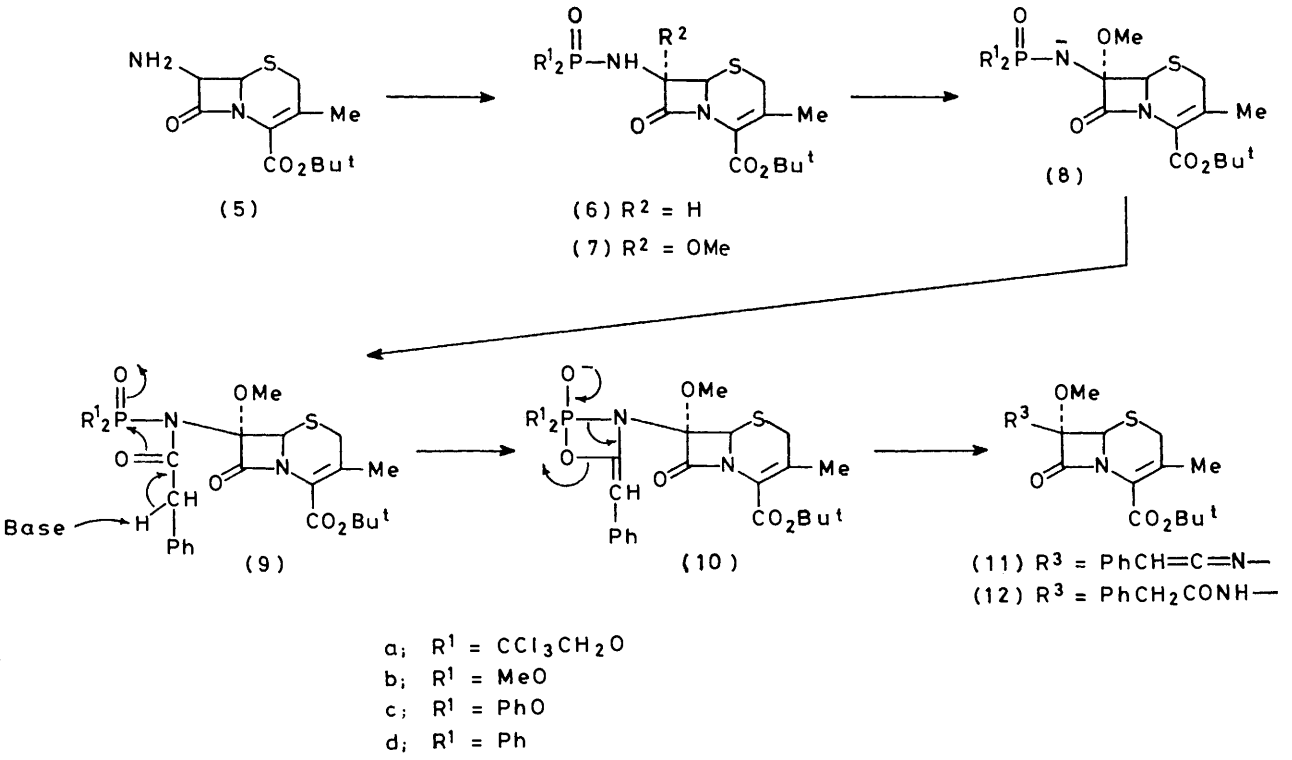
(13) $R^1 = R^2 = H$

(14) $R^1 = (CCl_3CH_2O)_2P(O)-$, $R^2 = H$

(15) $R^1 = (CCl_3CH_2O)_2P(O)-$, $R^2 = OMe$

(16) $R^1 = PhCH_2CO$, $R^2 = OMe$

with n-butyl-lithium and phenylacetyl chloride, showed that the reaction ceased immediately after the rapid formation of (11), while most of the starting material (7a) remained unchanged. These results imply that the low yield of (11) was probably due to incomplete formation of the amide anion (8a). This situation was overcome to a great extent when (7a) was treated with equimolar amounts of triethylamine and n-butyl-lithium[9] at −70 °C for 15 min, followed by addition of phenylacetyl chloride (method C). By this procedure the ketenimine (11) was obtained in 38% yield, together with a small quantity of 7α-methoxy-7β-phenylacetamide



(5) (6) $R^2 = H$ (7) $R^2 = OMe$ (8) (9) (10) (11) $R^3 = PhCH{=}C{=}N-$ (12) $R^3 = PhCH_2CONH-$

a; $R^1 = CCl_3CH_2O$
b; $R^1 = MeO$
c; $R^1 = PhO$
d; $R^1 = Ph$

SCHEME 2

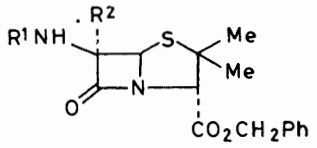
(12) (15%). The latter compound might have been produced by hydration of (11) during the work-up procedure. Other 7α-methoxy-7β-phosphoramidates, (7b) and (7c), were also converted into the ketenimine (11) and/or 7α-methoxy-7β-phenylacetamide (12) by this procedure. Treatment of 7α-methoxy-7β-phosphinamide (7d), however, resulted in recovery of starting material.

The stability of the ketenimine appears to depend on the nature of the substituent at C-3 of the cephem ring, because treatment of (15) by method C, followed by the usual work-up afforded, contrary to the result obtained with (7a), the desired diphenylmethyl 7α-methoxy-7β-phenylacetamidocephalosporanate (16) in 48% yield, without the corresponding ketenimine.

This method was also applied to the synthesis of 6α-methoxypenicillins. Thus 6-aminophenicillanate (17) was transformed to the 6β-phosphoramidate (18) * in 38% yield, which was converted into 6α-methoxy-6β-phosphoramidate (19) in 76% yield by the t-butyl hypochlorite method. Treatment of (19) by method C

* The synthesis of 6β-phosphoramidopenicillanic acids has been reported.[10]

afforded benzyl 6α-methoxy-6β-phenyl-acetamidopenicillanate (20) in 45% yield. Thus the reactions described above provide a new and simple method for the preparation of 7α-methoxycephalosporins and 6α-methoxypenicillins.



(17) $R^1 = R^2 = H$

(18) $R^1 = (CCl_3CH_2O)_2P(=O)-$, $R^2 = H$

(19) $R^1 = (CCl_3CH_2O)_2P(=O)-$, $R^2 = OMe$

(20) $R^1 = PhCH_2CO$, $R^2 = OMe$

EXPERIMENTAL

M.p.s were determined on a Yanagimoto melting point apparatus. I.r. spectra were recorded on a Hitachi type 215 spectrophotometer. N.m.r. spectra were taken on a Varian T-60 spectrometer and are reported in parts per million downfield from $SiMe_4$ (δ).

t-Butyl 7β-[*Bis*-2,2,2-*trichloroethyl*)*phosphoramido*]*deacetoxycephalosporanate* (6a).—To a stirred solution of t-butyl 7-aminodeacetoxycephalosporanate (5) (2.70 g) in methylene chloride (40 ml) was added pyridine (1.00 g) and bis-(2,2,2-trichloroethyl)phosphorochloridate (4.16 g) at room temperature. The reaction mixture was stirred for 2 h and washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogencarbonate, and water. The organic phase was dried with $MgSO_4$ and evaporated *in vacuo* to leave an oily residue. This oily residue was crystallized from ether to give (6a) (3.64 g), m.p. 162—163 °C (decomp.); $\nu_{max.}$ (KBr) 1 770 and 1 715 cm^{-1}; δ ($CDCl_3$) 1.52 (s, 9 H, Bu^t), 2.08 (s, 3 H, 3-Me), 3.38 (q, 2 H, 2-CH_2), 4.60 (s, 2 H, CCl_3CH_2), 4.72 (s, 2 H, CCl_3CH_2), 4.88 (d, 1 H, 6-H), and 5.25 (dd, 1 H, 7-H) (Found: C, 31.6; H, 3.3; N, 4.6. $C_{16}H_{21}Cl_6N_2O_6PS$ requires C, 31.3; H, 3.5; N, 4.6%).

Other 7β-phosphoramidates [(6b), (6c), and (14)], the 7β-phosphinamide (6d), and the 6β-phosphoramidate (18) were similarly prepared.

t-Butyl 7β-(*dimethylphosphoramido*)*deacetoxycephalosporanate* (6b). M.p. 77—78 °C (decomp.); $\nu_{max.}$ (KBr) 1 770 and 1 705 cm^{-1}; δ ($CDCl_3$) 1.50 (s, 9 H, Bu^t), 2.09 (s, 3 H, 3-Me), 3.38 (q, 2 H, 2-CH_2), 3.79 (s, 3 H, MeO), 3.87 (s, 3 H, MeO), 4.95 (d, 1 H, 6-H), and 5.17 (dd, 1 H, 7-H) (Found: C, 44.3; H, 5.9; N, 7.2. $C_{14}H_{23}N_2O_6PS$ requires C, 44.4; H, 6.1; N, 7.4%).

t-Butyl 7β-(*diphenylphosphoramido*)*deacetoxycephalosporanate* (6c). M.p. 187—188 °C (decomp.); $\nu_{max.}$ (KBr) 1 760 and 1 705 cm^{-1}; δ ($CDCl_3$) 1.55 (s, 9 H, Bu^t), 2.09 (s, 3 H, 3-Me), 3.28 (d, 2 H, 2-CH_2), 4.18 (d, 1 H, NH), 4.85 (d, 1 H, 6-H), 5.38 (q, 1 H, 7-H), and 7.30 (s, 10 H, 2 Ph) (Found: C, 57.1; H, 5.3; N, 5.6. $C_{24}H_{27}N_2O_6PS$ requires C, 57.4; H, 5.4; N, 5.6%).

t-Butyl 7β-(*diphenylphosphinamido*)*deacetoxycephalosporanate* (6d). M.p. 185—188 °C (decomp.); $\nu_{max.}$ (KBr) 1 750 and 1 695 cm^{-1}; δ ($CDCl_3$) 1.53 (s, 9 H, Bu^t), 2.07 (s, 3 H, 3-Me), 3.40 (q, 2 H, 2-CH_2), 4.90 (d, 1 H, 6-H), 5.14 (dd, 1 H, 7-H), 7.30—8.40 (m, 10 H, 2 Ph) (Found: C, 61.5; H, 6.0; N, 5.9. $C_{24}H_{27}N_2O_4PS$ requires C, 61.3; H, 5.8; N, 6.0%).

Diphenylmethyl 7β-[*bis*-(2,2,2-*trichloroethyl*)*phosphoramido*]*cephalosporanate* (14). An amorphous solid; $\nu_{max.}$ (KBr) 1 780 and 1 710 cm^{-1}; δ ($CDCl_3$) 1.98 (s, 3 H, OCOMe), 3.41 (br s, 2 H, 2-CH_2), 4.64 (d, 2 H, CCl_3CH_2), 4.73 (d, 2 H, CCl_3CH_2), 4.80 (m, 4 H, 3-CH_2, 6-H, and 7-H), 6.92 (s, 1 H, CO_2CH), and 7.33 (s, 10, 2 Ph).

Benzyl 6β-[*bis*-(2,2,2-*trichloroethyl*)*phosphoramido*]*penicillanate* (18). An amorphous solid; $\nu_{max.}$ (KBr) 1 770 and 1 730 cm^{-1}; δ ($CDCl_3$) 1.40 (s, 3 H, 2-CH_2), 1.60 (s, 3 H, 2-Me), 4.47 (s, 1 H, 3-CH), 4.60 (d, 2 H, CCl_3CH_2), 4.71 (d, 2 H, CCl_3CH_2), 4.95 (dd, 1 H, 6-H), 5.17 (s, 2 H, CO_2CH_2), 5.55 (d, 1 H, 5-H), and 7.33 (s, 5, Ph).

t-Butyl 7β-[*Bis*-(2,2,2-*trichloroethyl*)*phosphoramido*]-7α-*methoxydeacetoxycephalosporanate* (7a).—To a stirred solution of (6a) (7.56 g) in dry tetrahydrofuran (50 ml) at −78 °C under nitrogen was added a solution of lithium methoxide in methanol [prepared from lithium metal (316 mg) and methanol (35 ml)] and the mixture was stirred for 5 min. To the stirred solution was added t-butyl hypochlorite (1.46 g) at −78 °C and the solution was stirred for 30 min. The reaction was quenched at −78 °C with acetic acid (3 ml). The reaction mixture was poured into a saturated aqueous solution of sodum bicarbonate and extracted with ethyl acetate. The organic phase was separated, washed with water, dried with $MgSO_4$, filtered, and evaporated. The residue was crystallized from ether to give (7a) (7.37 g).

Other 7α-methoxy-derivatives [(7b), (7c), (7d), (15), and (19)] were similarly prepared. Their analysis and physical data are summarized in the Table.

t-Butyl 7α-*Methoxy*-7β-(*phenylketenimino*)*deacetoxycephalosporanate* (11).—*Method A*. To a stirred solution of (7a) (305 mg) in DMF (10 ml) at −20 °C under nitrogen was added sodium hydride (13 mg). The mixture was stirred for 30 min and phenylacetyl chloride (80 mg) was added. The reaction mixture was diluted with ethyl acetate, washed with water, dried with $MgSO_4$, and evaporated. The oily residue was purified by silica gel chromatography using chloroform as eluant to give (11) (30 mg, 15%), m.p. 121—123 °C (decomp.); $\nu_{max.}$ (KBr) 2 000, 1 760, and 1 720 cm^{-1}; δ ($CDCl_3$) 1.55 (s, 9 H, Bu^t), 2.14 (3 H, 3-Me), 3.18 (s, 2 H, 2-CH_2), 3.69 (s, 3 H, 7-OMe), 4.99 (s, 1 H, 6-H), 5.22 (s, 1 H, CH=), and 7.25 (s, 5 H, Ph) (Found: C, 62.8; H, 5.8; N, 6.9. $C_{21}H_{24}N_2O_4S$ requires C, 63.0; H, 6.0; N, 7.0%).

Method B. To a solution of (7a) (305 mg) in tetrahydrofuran (10 ml) at −78 °C under nitrogen was added a 9% solution of n-butyl-lithium in n-hexane (0.45 ml). The mixture was stirred at −78 °C, phenylacetyl chloride (80 mg) was added, and the resulting mixture was stirred at −78 °C under nitrogen for 30 min. The reaction mixture was diluted with ethyl acetate, washed with water, dried with $MgSO_4$, and evaporated *in vacuo* to leave an oil. This oil was purified by silica gel chromatography using chloroform as eluant to give (11) (20 mg, 10%).

Method C. To a solution of (7a) (610 mg) in tetrahydrofuran (20 ml) at −78 °C under nitrogen was added triethylamine (100 mg) and a 9% solution of n-butyl-lithium in n-hexane (0.9 ml). The reaction mixture was stirred for 15 min and phenylacetyl chloride (160 mg) was added. The resulting mixture was diluted with ethyl acetate, washed with water, dried with $MgSO_4$, and evaporated *in*

Analysis and physical data of (7a—d), (15), and (19)

	M.p. (°C) *	$\nu_{max.}$ (KBr)/ cm^{-1}	δ (60 MHz, $CDCl_3$)	Analysis (%)
(7a)	137—138	1 750, 1 710	1.53 (s, 9 H, Bu^t), 2.16 (s, 3 H, 3-Me), 3.26 (s, 2 H, 2-CH_2), 3.65 (s, 3 H, 7-OMe), 4.68 (d, 2 H, CCl_3CH_2), 4.76 (d, 2 H, CCl_3CH_2), 4.94 (s, 1 H, 7-H), 5.00 (d, 1 H, NH)	Found: C, 31.9; H, 3.5; N 4.4. $C_{17}H_{23}Cl_6N_2O_7PS$ requires C, C, 31.7; H, 3.6; N, 4.4.
(7b)	125—126	1 750, 1 700	1.54 (s, 9 H, Bu^t), 2.16 (s, 3 H, 3-Me), 3.15 (br s, 2 H, 2-CH_2), 3.56 (s, 3 H, 7-OMe), 3.71 (d, 3 H, MeO), 3.87 (d, 3 H, MeO), 4.86 (s, 1 H, 6-H)	Found: C, 44.5; H, 6.2; N, 6.8. $C_{15}H_{25}N_2O_7PS$ requires C, 44.1; H, 3.6; N, 6.9.
(7c)	120—121	1 750, 1 700	1.50 (s, 9 H, Bu^t), 2.14 (s, 3 H, 3-Me), 3.03 (br s, 2 H, 2-CH_2), 3.52 (s, 3 H, 7-OMe), 4.83 (s, 1 H, 6-H), 5.21 (d, 1 H, NH), 7.23 (s, 10, 2 Ph)	Found: C, 56.7; H, 5.6; N, 5.3. $C_{25}H_{29}N_2O_7PS$ requires C, 56.4; H, 5.5; N, 5.3.
(7d)	132—133	1 750, 1 700	1.49 (s, 9 H, Bu^t), 2.10 (s, 3 H, 3-Me), 3.31 (s, 2 H, 2-CH_2), 3.32 (s, 3 H, 7-OMe), 4.50 (d, 1 H, NH), 4.88 (s, 1 H, 6-H), 7.30—8.40 (m, 10 H, 2 Ph)	Found: C, 60.5; H, 5.9; N, 5.6. $C_{25}H_{29}N_2O_5Ps$ requires C, 60.0; H, 5.8; N, 5.6.
(15)	104—106	1 780, 1 740, 1 710	2.01 (s, 3 H, OCOMe), 3.43 (s, 2 H, 2-CH_2), 3.77 (s, 3 H, 7-OMe), 4.66 (d, 2 H, CCl_3CH_2), 4.80 (d, 2 H, CCl_3CH_2), 4.98 (s, 1 H, 6-H), 4.98 (q, 2 H, 3-CH_2), 6.98 (s, 1 H, CO_2CH), 7.35 (s, 10 H, 2 Ph)	Found: C, 41.7; H, 3.4; N, 3.7. $C_{28}H_{27}Cl_6N_2O_9PS$ requires C, 41.5; H, 3.4; N, 3.5.
(19)	123—125	1 775, 1 740	1.36 (s, 3 H, 2-Me), 1.52 (s, 3 H, 2-Me), 3.56 (s, 3 H, 6-OMe), 4.55 (d, 2 H, CCl_3CH_2), 4.72 (s, 1 H, 3-H), 4.76 (d, 2 H, CCl_3CH_2), 5.18 (s, 1 H, CO_2CH), 5.23 (d, 1 H, NH), 5.50 (s, 1 H, 5-H), 7.34 (s, 5 H, Ph)	Found: C, 35.6; H, 3.1; N, 4.3. $C_{20}H_{23}Cl_6N_2O_7PS$ requires C, 35.4; H, 3.4; N, 4.1.

* All compounds decomposed.

vacuo to leave an oil. This oil was purified by silica gel chromatography using chloroform as eluant to give (11) (152 mg, 38%) and (12) (63 mg, 15%).

Treatment of (7b) by method C afforded (12) (44%); from (7c) were obtained (11) (36%) and (12) (22%).

t-Butyl 7α-Methoxy-7β-(phenylacetamido)deacetoxycephalosporanate (12).—To a solution of (11) (10 mg) in acetone (1 ml) was added 1N hydrochloric acid (0.1 ml) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was dried with $MgSO_4$ and evaporated *in vacuo* to give (12) (8 mg), which was identical by n.m.r. and i.r. (KBr) spectra with an authentic sample.[3c]

Diphenylmethyl 7α-Methoxy-7β-(phenylacetamido)cephalosporanate (16).—To a stirred solution of (15) (811 mg) in tetrahydrofuran (10 ml) at −78 °C under nitrogen were added triethylamine (100 mg) and a 9% solution of n-butyllithium in n-hexane (0.5 ml). The reaction mixture was stirred for 15 min and phenylacetyl chloride (154 mg) was added. The mixture was stirred for 30 min at −78 °C, and the resulting mixture was poured into ice–water and extracted with ethyl acetate. The organic phase was washed with water, dried with $MgSO_4$, evaporated *in vacuo*, and the residue purified by silica gel chromatography (chloroform eluant) to give (16) (270 mg, 48%) as a colourless residue; $\nu_{max.}$ (KBr) 1 780 and 1 710 cm^{-1}; δ ($CDCl_3$) 1.96 (s, 3 H, OCOMe), 3.34 (br s, 2 H, 2-CH_2), 3.39 (s, 3 H, 7-OMe), 3.59 (s, 2 H, CH_2CO), 4.86 (q, 2 H, 3-CH_2), 5.01 (s, 1 H, 6-H), 6.89 (s, 1 H, CO_2CH), and 7.24 (br s, 15 H, 3 Ph); this sample was identical (n.m.r. and i.r. spectra) with an authentic sample obtained from diphenylmethyl 7β-(phenylacetamido)cephalosporanate by the known method.[3h]

Benzyl 6α-Methoxy-6β-(phenylacetamido)penicillanate (20).—The procedure for the preparation of (16) was carried out using (19) (679 mg) instead of (15). Compound (20) was obtained (184 mg, 45%) as a colourless residue which was identical [n.m.r. and i.r. (KBr) spectra] with an authentic sample obtained by the known method.[3e]

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