SYNTHETIC STUDIES IN THE FIELD OF NATURAL PRODUCTS

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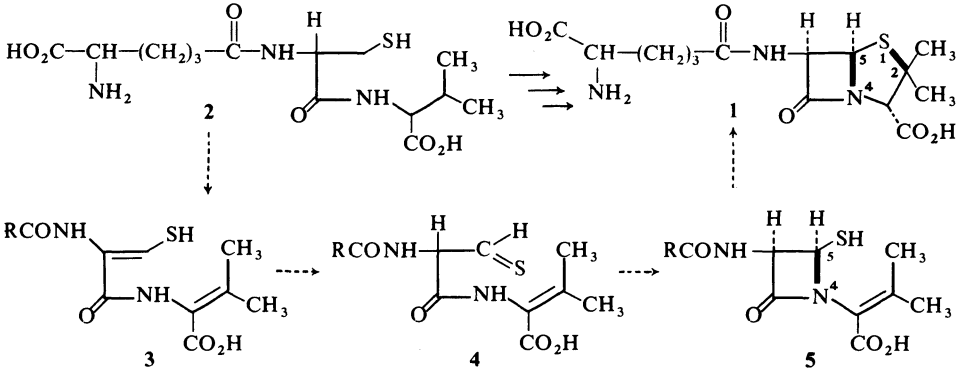
ABSTRACT

The bicyclic deacetoxy-7-methoxycephalosporin derivative **70** and 6-methoxypenicillin derivative **63** were synthesized from an acyclic tripeptide equivalent **60** with control of stereochemistry.

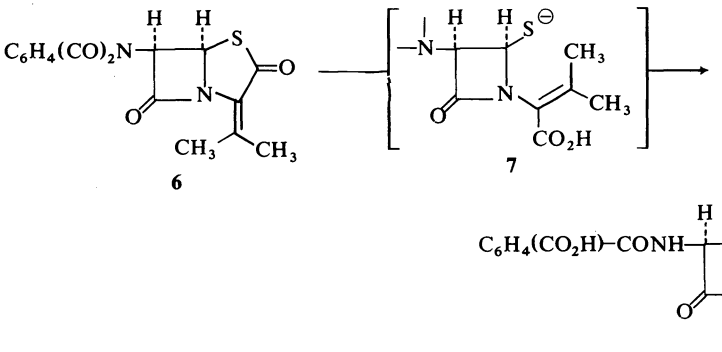
Several magnificent total syntheses of the penicillin–cephalosporin antibiotics have been completed[1], but to our knowledge none of them was achieved on the basis of the biosynthetic pathways of the antibiotics. This paper is concerned with a 'biogenetic-type' synthesis of the bicyclic penicillin–cephalosporin antibiotics from an acyclic tripeptide equivalent.

According to extensive studies[2] bicyclic isopenicillin N **1** is biosynthesized from the so-called 'Ernstein tripeptide,' δ-(α-aminoadipyl)systeinylvaline **2**. In this transformation, two bonds, i.e. the 1–2 bond and the 4–5 bond, are created. One of the most attractive suggestions for these bond creation processes involves oxidation of the tripeptide **2** to the dehydrosteinyl derivative **3**, tautomerization of **3** to the thioaldehyde **4** and cyclization between the thioaldehyde and the amide groups to generate a highly strained β-lactam thiol **5**. The second, i.e. 1–2 bond is formed simply by conjugated addition of the thiol group to the dehydrovaline moiety, generated from the valine part of **2** before or after the β-lactam thiol system of **5** is formed.

Concerning the second process, the 1–2 bond formation was realized *by chemical synthesis.* Wolfe and his co-workers[3] succeeded in converting

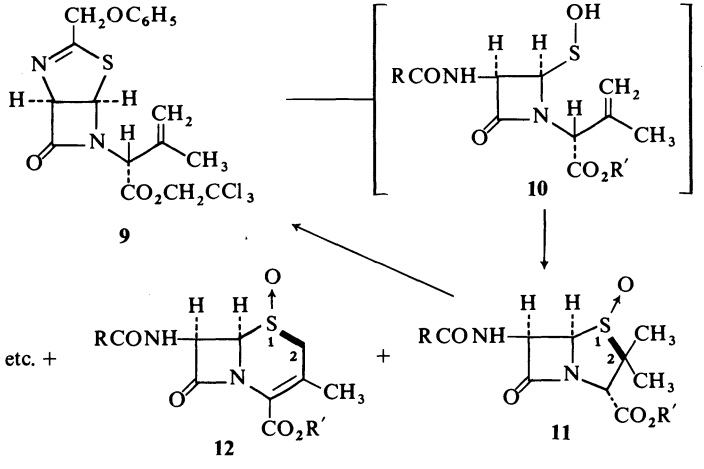


phthalimidoanhydropenicillin **6**, a degradation product of penicillin, into the penicillin **8** under carefully controlled basic conditions. The reaction probably proceeded through an intermediate **7**, generated by hydrolysis of the thiolactone group in **6**. On conjugated addition, the stereochemistry at the 3-position was controlled in the desired sense (D-configuration) for steric reasons.

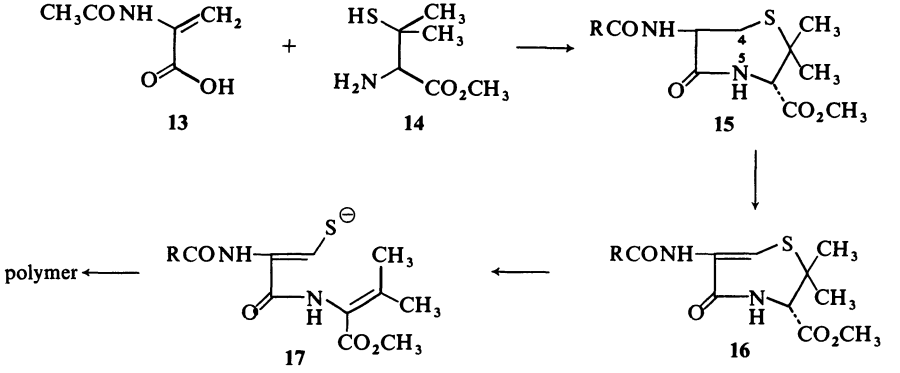


The second realization of the 1–2 bond formation by chemical synthesis was achieved by Cooper[4] in 1972. Namely, he degraded[5] penicillin sulphoxide **11** to β-lactam thiazoline derivative **9** and then brought **9** back to a mixture of penicillin sulphoxide **11**, cephalosporin sulphoxide **12**, and other substances, by *m*-chloroperbenzoic acid oxidation in the presence of trifluoroacetic acid. He proposed that the reaction proceeded through sulphenic acid intermediate **10**.

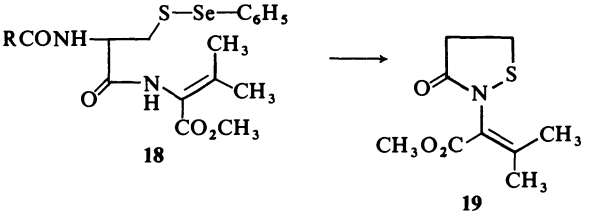
In contrast to the very successful realization of the 1–2 bond formation, the 4–5 bond has not been created *by chemical synthesis* until now, although several intelligent attempts have been made. For instance, Leonard and his co-workers[6] published a series of papers in the 1960s in which they described a synthesis of the seven-membered lactam **15** from *N*-acetyl dehydroalanine



13 and methyl pencillamine **14**. On oxidation of **15** with chlorine, dehydrochlorination rather than bond formation between the 4 and 5 positions took place, to give compound **16**. Basic treatment of **16** afforded the sodium salt of the mercaptide **17**, which corresponds to the enol form of the thioaldehyde **4**. But, on acidification, compound **17** polymerized and no desired cyclization between the thioaldehyde and the amide groups was observed.

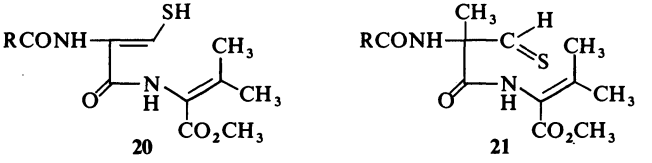


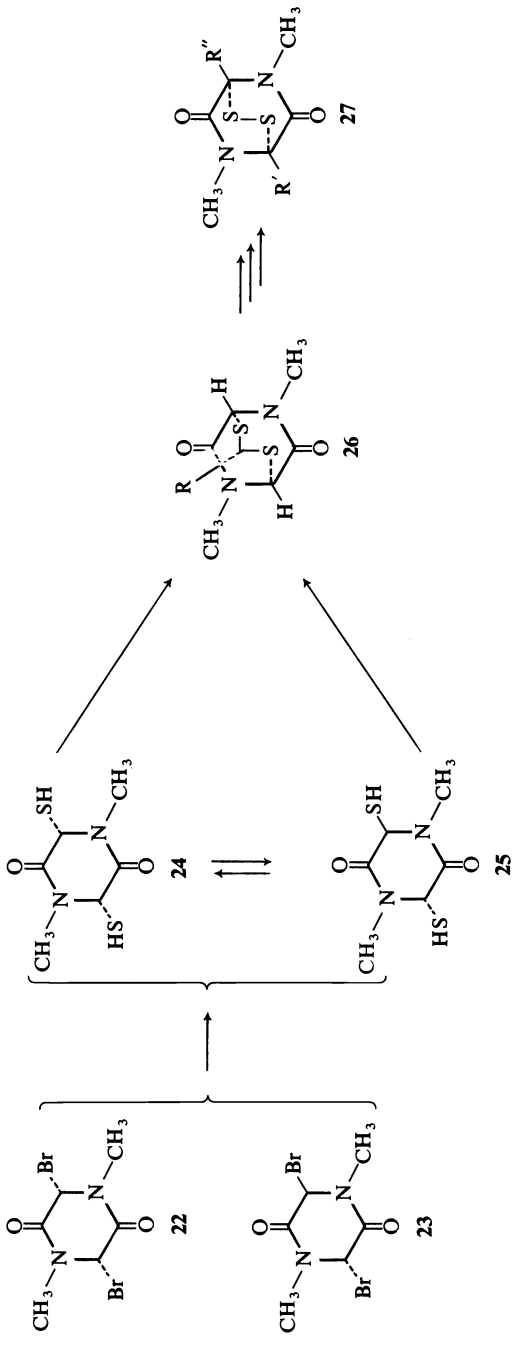
Recently Baldwin and his co-workers[7] attempted a synthesis of the thioaldehyde **4** from the selenide **18** by oxidation but the reaction followed a direction more or less similar to Leonard's observations[6], yielding compound **19**.



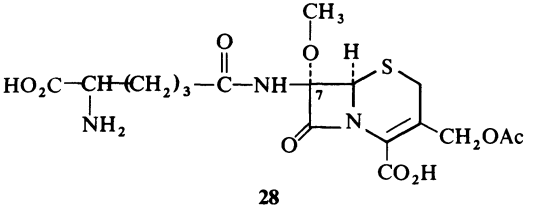
Scott, Young and their co-workers[8] have synthesized the thioaldehydes **20** (as its enol form) and **21** under a large variety of conditions, but observed none of the expected spontaneous cyclization to the β-lactam ring system.

Our strategy, which for the most part is an extension of our recent synthetic studies[9] on epidithiodiketopiperazines **27**, is briefly summarized as follows. The functionalities of some of the synthetic intermediates of epidithiodiketopiperazines are similar to those of the compound proposed for penicillin biosynthesis. For instance, an amide carbonyl, an amide nitrogen and





a carbon atom bearing a thiol group are present in a contiguous series in compound **24**, which is exactly the same as in compound **5**. It was encouraging that a compound having the required functionalities is available as an isolable, stable and well-characterized substance at least in one case familiar to us. For a stereospecific synthesis of epidithiodiketopiperazines **27**, two asymmetric centres in **24** were fixed as *cis* by thioacetalization. It was interesting that the thiocetal **26** was obtained from *trans*-dithiol **25** with the same ease and in the same yield as from *cis*-dithiol **24**. These results indicate that a rapid epimerization at the asymmetric centres is operative under the thioacetalization condition, i.e. a catalytic amount of boron trifluoride etherate in methylene chloride at room temperature. There could be several possible mechanistic explanations for the epimerization: enolization of the amide carbonyl group, or elimination and addition of hydrogen sulphide would account for this phenomenon. A third possibility, though obviously less probable, is that epimerization takes place in a ring-opening and -closing mechanism, via a thioaldehyde–amide intermediate. The ring-closing process of this latter mechanistic possibility corresponds to the bond formation process required for the biosynthesis of penicillin, i.e. **4** → **5**. The six-membered ring size of **24** and **25** is ideal for such a cyclization, but some additional factors assisting ring-closure could also give a strained β-lactam system. A methoxy group at the 6-position in the penam- or at the 7-position in the cephem-ring system could be such an additional factor, firstly because 7-methoxycephalosporin C **28** is actually a naturally occurring antibiotic[10],



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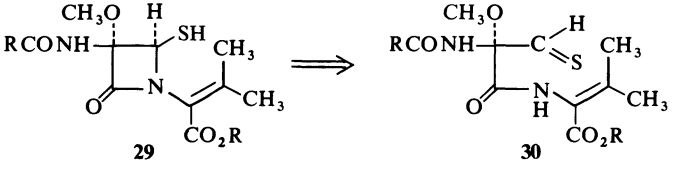
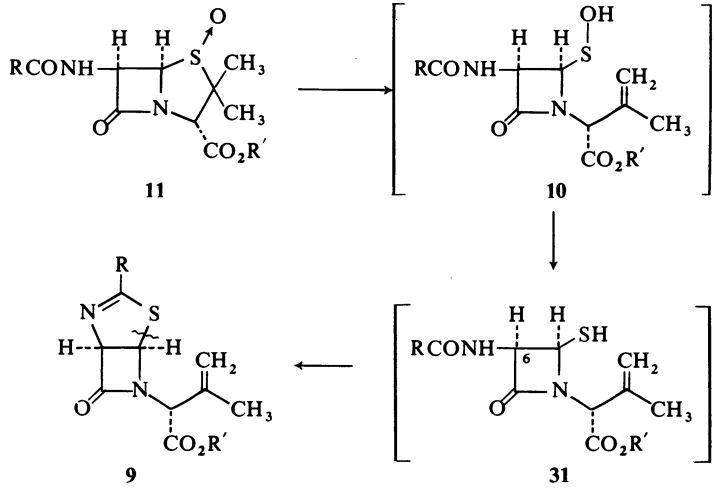
and secondly because it is well known that a higher degree of substitution on the ring element assists the formation of a small ring system. Furthermore, the methoxy group would also eliminate complications related to enolization of the thioaldehyde group. From these considerations, the **29** → **30** disconnection would be one of the possibilities for the synthesis of a type **5** compound.

Let us consider the stereochemical problems of two asymmetric centres in **29**. As we noted before, Cooper and Jose[5] synthesized β-lactam thiazoline **9** by reductively trapping sulphenic acid **10**, generated from penicillin sulphoxide **11**. The intermediate of this reaction was proposed to be the thiol **31**

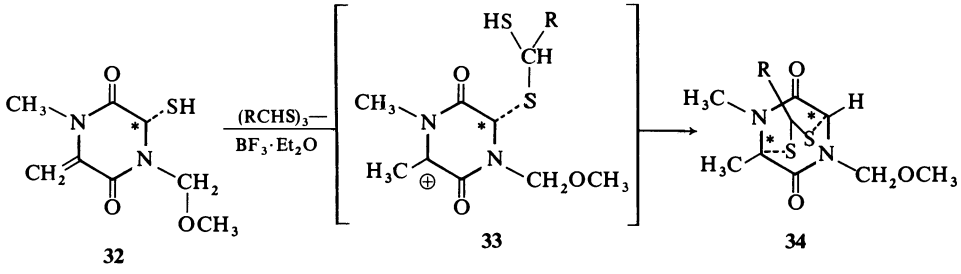


29 **30**

which cyclized intramolecularly to the secondary amide function at the 6-position. This result suggests that there would be no reason to differentiate the thiol **31** from the thiazoline **9** *at least in the chemical synthesis.* If we agree with this argument, we will recognize an interesting disconnection for the synthesis of β-lactam thiazoline **9**, which is indicated by a wavy line in structure **9**. The advantage of using this disconnection is that there now

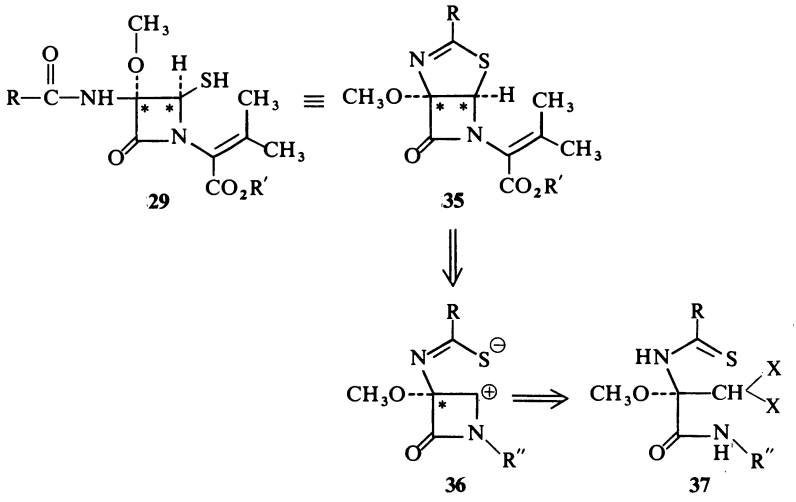


exists a possibility to control the stereochemistry of the two asymmetric centres via **36**. Such control of stereochemistry has already been demonstrated in our synthesis of epidithiodiketopiperazine **34** from **32**[9]. The probable intermediate in the conversion of **32** to **34** is the carbonium ion **33**, which is intramolecularly trapped by the hemidithioacetal.



From these considerations, one of the attractive possibilities for a biogenetic-type synthesis of the penicillin–cephalosporin antibiotics could be the one shown below. The most crucial step in this proposal is the creation of the β-lactam thiazoline **35**. Therefore we started to study a double cyclization reaction, i.e. **37** → **35**, using model compounds.

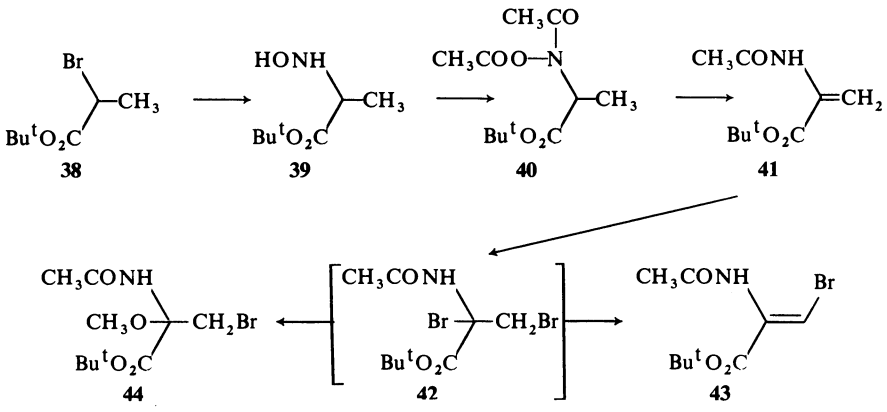
tert-Butyl bromopropionate[11] **38** ($b.pt_{21}$, 68–70°C) was converted to the hydroxylamine **39** (m.pt, 74–75°C) by a standard procedure in 85 per cent yield. Acetic anhydride treatment of **39** at 100°C for 30 min yielded the



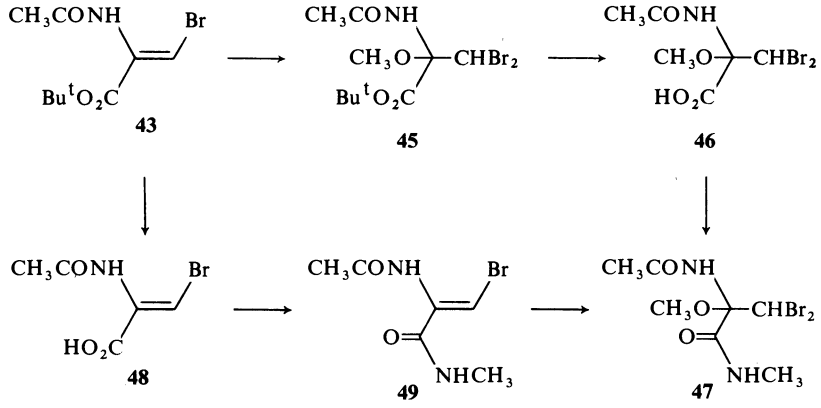
diacetate **40** (oil), which was converted to *N*-acetyldehydroalanine *tert*-butyl ester **41**—oil $\delta^{CDCl_3}_{p.p.m.}$, 1.53 (9H, s), 2.13 (3H, s), 5.89 (1H, s), 6.61 (1H, s) and 7.96 (1H broad s)—by triethylamine treatment in 72 per cent over-all yield from **39**.

The following description is limited only to the *N-acetyl*dehydroalanine derivatives, but it is possible to introduce a different acyl group on the nitrogen atom simply by changing the acylating reagent at this stage.

Molecular bromine reacts smoothly with the acylenamine system of **41** in methylene chloride at room temperature, to give the dibromide **42**, which is non-isolable but clearly detectable by n.m.r. analysis. Triethylamine treatment of **42** gave the *N*-acetylbromodehydroalanine *tert*-butyl ester **43** (m.pt, 106–107°C) in 90 per cent over-all yield from **41**. On the other hand, addition of methanol to the methylene chloride solution of the dibromide **42** gave the methoxy monobromide **44** in high yield. These reactions, i.e. **42** → **43** and **42** → **44**, presumably proceed via a ketimine intermediate.

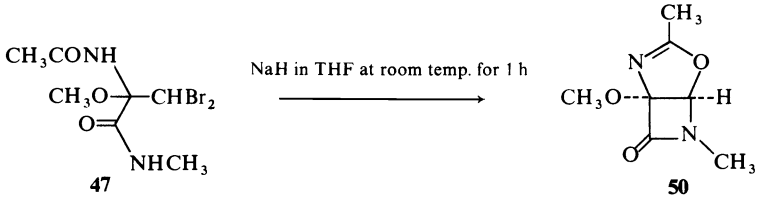


Repeating the same reaction on bromodehydroalanine *tert*-butyl ester **43** yielded the methoxy dibromide *tert*-butyl ester **45** (m.pt, 115–116°C) in 82 per cent yield. Removal of the carboxylic acid blocking group of **45** under acidic conditions gave the methoxy dibromo acid **46** (m.pt, 143–144°C) in 80 per cent yield. A standard DCC procedure on **46** with methylamine in dioxane at room temperature afforded the methoxy dibromo diamide **47**—m.pt, 114–115°C; $\delta^{CDCl_3}_{p.p.m.}$, 2.09 (3H, s), 2.97 (3H, d, J = 5 Hz), 3.33 (3H, s), 6.67 (1H, s), 6.82 (1H, broad s) and 7.08 (1H, broad s); ν^{KBr}_{max}, 3300, 1690, 1670, 1495 cm^{-1}—in 74 per cent yield. The diamide **47** could also be synthesized from **43** through the acid **48** (m.pt, 142°C decomp) and the diamide **49** (m.pt, 145–146°C decomp) in better over-all yield (60 per cent).



The methoxy dibromo diamide **47** is a suitable model compound to study the crucial double cyclization *in the oxygen series*. Thus, when the diamide **47** was treated with about two equivalents of sodium hydride in tetrahydrofuran at room temperature for 1.5 h, a remarkably clean reaction was observed. This was demonstrated by the n.m.r. spectrum (*Figure 1*) of the crude product. The yield of the crude product was about **70** per cent. The crystalline substance (m.pt, 84–85°C) was isolated in around **40** per cent yield.

Structure **50** was assigned to the product from analysis of the spectroscopic data—$\delta^{CDCl_3}_{p.p.m.}$, 2.13 (3H, s), 2.91 (3H, s), 3.58 (3H, s) and 5.56 (1H, s); $\nu^{CH_2Cl_2}_{max}$, 1785 and 1650 cm^{-1}; ν^{KBr}_{max} 1770 and 1640 cm^{-1}—and the elemental analysis —found: C, 49.29, H, 5.86, N. 16.38; calcd for $C_7H_{10}O_3N_2$: C, 49.40, H. 5.92, N, 16.46. In particular, the carbonyl absorption of the i.r. spectra is characteristic for the presence of the β-lactam oxazoline ring system.



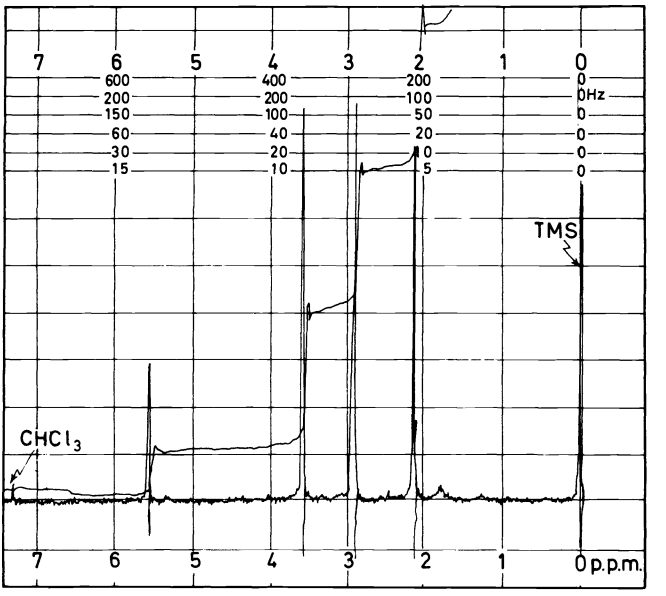
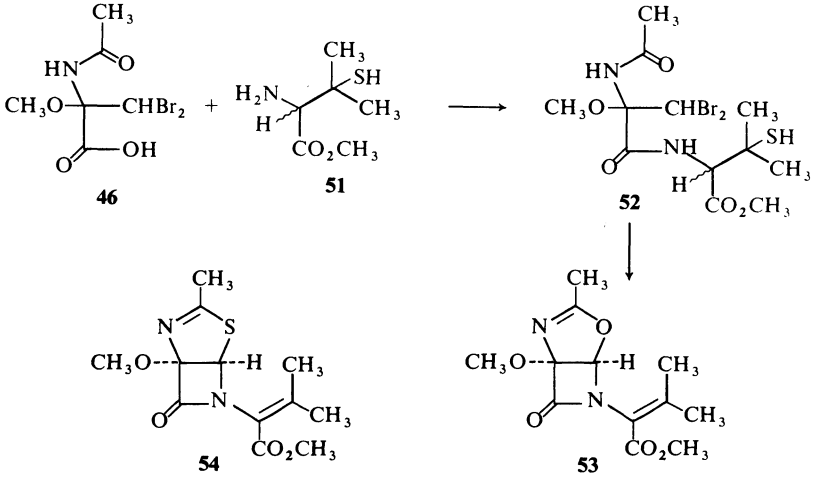


Figure 1. N.m.r. spectrum of the crude product of **50**.

Studies on the reaction mechanisms, the scope and limitation, and application of the double cyclization reaction to a synthesis of a variety of compounds containing β-lactam ring systems are currently in progress in our laboratories, but the present paper is only concerned with an extension of the reaction to a biogenetic-type synthesis of the penicillin–cephalosporin antibiotics. Along this line, the double cyclization reaction was examined on the tripeptide equivalent **52**.

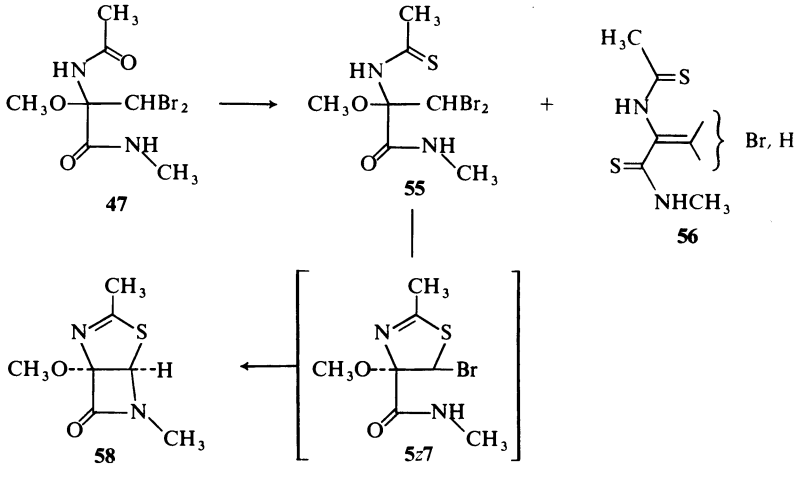
Since several attempts to condense the methoxy dibromo acid **46** with dehydrovaline methyl ester were not promising, a condensation reaction



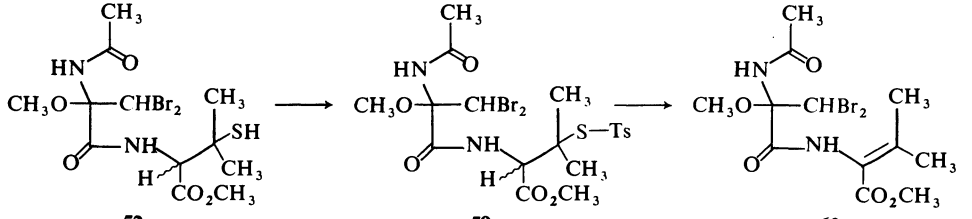
was carried out on the acid **46** with penicillamine methyl ester **51**. In the latter case, the condensation product **52** (m.pt, 159–160°C as a diastereomeric mixture) was obtained in 60 per cent yield by a standard DCC procedure. Sodium hydride in tetrahydrofuran at room temperature caused excellent double cyclization, and furthermore, elimination of hydrogen sulphide from the penicillamine moiety to yield the β-lactam oxazoline **53** (oil) occurred in around 40 per cent yield. The structure of the product was strongly supported by the fact that the spectroscopic data—$\delta_{p.p.m.}^{CDCl_3}$, 1.86 (3H, s), 2.14 (3H, s), 2.28 (3H, s), 3.63 (3H, s), 3.79 (3H, s) and 5.88 (1H, s); $\nu_{max}^{CH_2Cl_2}$, 1 785, 1 728 and 1 650 cm^{-1}—agreed with data for authentic β-lactam thiazoline **54**.

Let us examine the double cyclization reaction *in the sulphur series*. For this purpose we need the methoxy dibromo monothioamide **55**. The synthesis of the required monothioamide **55** turned out to be rather difficult. After several unsuccessful attempts, we could synthesize the desired monothioamide **55** from the diamide **47** by phosphorus pentasulphide in tetrahydrofuran at 50°C for 2 h in about 30 per cent yield. One of the by-products in this reaction was the dithioamide **56** (about 5 per cent yield). The desired monothiamide **55** was found to be an unstable substance; its half-life at room temperature was around 2 h. The double cyclization reaction was carried out on **55** with sodium hydride in tetrahydrofuran *without* the most careful precautions to exclude moisture from the reaction vessel. The major product isolated was the β-lactam oxazoline **50**, the formation of which could be best understood as the result of hydrolysis of the thioamide group of **55** via the intermediate **57**. Nevertheless, the desired β-lactam thiazoline **58**—oil; $\delta_{p.p.m.}^{CDCl_3}$, 2.36 (3H, s), 2.88 (3H, s), 3.57 (3H, s) and 5.75 (1H, s); $\nu_{max}^{CH_2Cl_2}$, 1 775 cm^{-1}—could be synthesized in about 5 per cent over-all yield from **47**, when the cyclization was carried out *with* the most careful precautions to exclude moisture from the reaction vessel.

Let us now take a look at the double cyclization reaction in the real case. The peptide **52**, synthesized from the methoxy dibromo acid **46** and penicillamine methyl ester **51**, slowly loses hydrogen sulphide to generate the

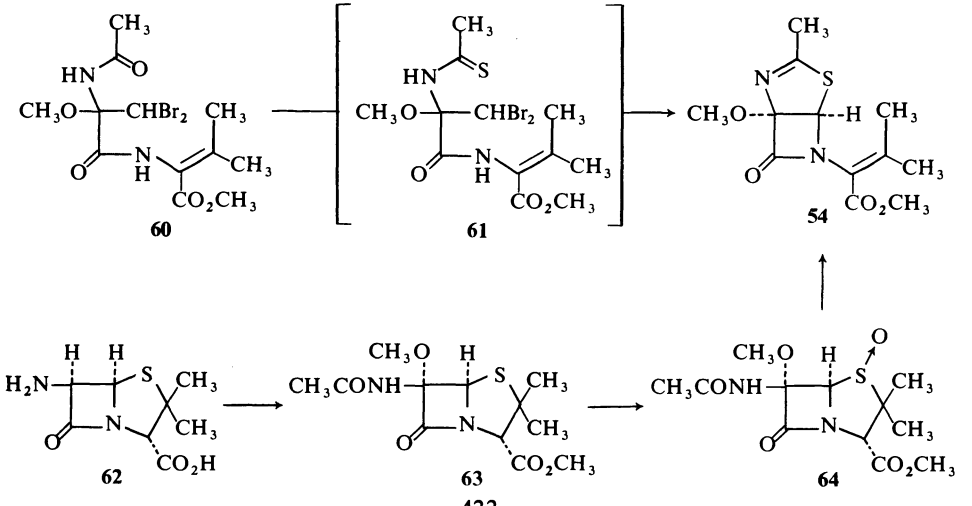


dehydrovaline derivative **60**—m.pt, 150–151°C; $\delta^{CDCl_3}_{p.p.m.}$, 2.02 (3H, s), 2.12 (3H, s), 2.26 (3H, s), 3.43 (3H, s), 3.79 (3H, s), 6.87 (1H, s), 7.20 (1H, broad s) and 7.96 (1H, broad s). Compound **60** was more efficiently prepared from the peptide **52** in the following manner. Compound **52** was converted under standard conditions (tosyl chloride and pyridine at room temperature) to the tosylate **59**, which gave the dehydrovaline derivative **60** in refluxing triethylamine. The over-all yield from **52** to **60** was 45 per cent.



52 **59** **60**

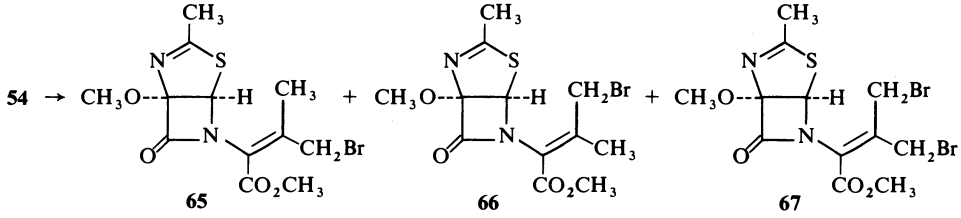
The dehydrovaline derivative **60** was treated with phosphorus pentasulphide in tetrahydrofuran at 50°C for 2 h and the unpurified reaction mixture was subjected to the double cyclization reaction under sodium hydride conditions immediately because we suspected that the desired monothioamide **61** might be unstable, judging from the results obtained in the model experiments. A preparative t.l.c. separation of the products on aluminium oxide plates gave the desired β-lactam thiazoline derivative **54** (oil) in about 12 per cent over-all yield from the dehydrovaline derivative **60**. The synthetic substance was identical with an authentic sample, synthesized from 6-aminopenicillanic acid **62** by following Koppel's[12] and then Cooper's[5] procedures (**62** → **63** → **64** → **54**) by comparison of n.m.r.—$\delta^{CDCl_3}_{p.p.m.}$, 1.83 (3H, s), 2.28 (3H, s), 2.38 (3H, s), 3.62 (3H, s), 3.80 (3H, s) and 5.80 (1H, s)—i.r. ($\nu_{max}^{CH_2Cl_2}$, 1775, 1728 and 1618 cm^{-1}), t.l.c. (aluminium oxide and silica gel plates) and high-pressure chromatography (analytical corasil-I).



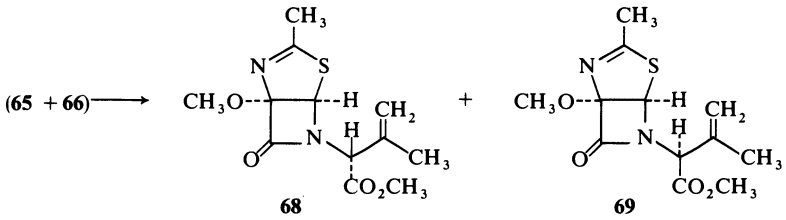
60 **61** **54**

62 **63** **64**

One of the possible ways to convert compound **54** to the penam- and cephem-ring systems would be to take advantage of Cooper's reaction[4], i.e. **9** → **11** + **12**. For this purpose, the conjugated double bond in **54** had to be moved to a deconjugated position; this was easily realized in the following way. *N*-Bromosuccinimide bromination of **54** in the presence of a small amount of α,α′-azobisisobutylnitrile in carbon tetrachloride at 75°C for 1.5 h, followed by a preparative t.l.c. separation of the products on aluminium oxide plates gave the monobromides **65** and **66** (70 per cent yield), the dibromide **67** (10 per cent yield) and the starting material **54** (10 per cent).



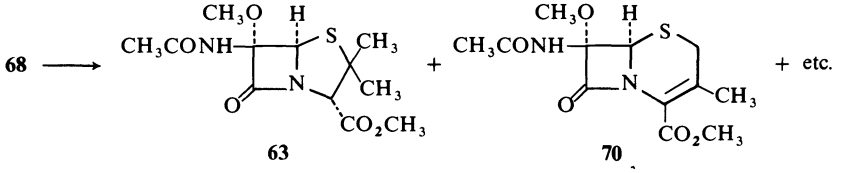
Zinc–acetic acid reduction of the monobromides **65** and **66** at room temperature for 25 min gave the deconjugated ester with *natural* configuration **68**—oil; $\delta^{CDCl_3}_{p.p.m.}$, 1.84 (3H, d, J = 1 Hz), 2.35 (3H, s), 3.58 (3H, s), 3.80 (3H, s), 4.93 (1H, s), 5.01 (1H, s), 5.16 (1H, q, J = 1 Hz) and 5.84 (1H, s)—the deconjugated ester with unnatural configuration **69**—oil; $\delta^{CDCl_3}_{p.p.m.}$, 1.85 (3H, d, J = 1 Hz), 2.38 (3H, s), 3.58 (3H, s), 3.80 (3H, s), 4.91 (1H, s), 5.15 (1H, s), 5.27 (1H, q, J = 1 Hz) and 5.62 (1H, s)—and the conjugated ester **54** in 90 per cent yield. The structure **68** for the monobromide with *natural* configuration was determined by comparison of the synthetic substance with the authentic sample, synthesized from 6-aminopenicillanic acid **62** by known methods[5, 13].



The ratio (68 : 69 : 54) of these components was about (3 : 4 : 5), but this is not a serious problem for synthetic purposes, because **69** can be easily isomerized to **54** by triethylamine treatment and the conjugated ester **54** can be recycled.

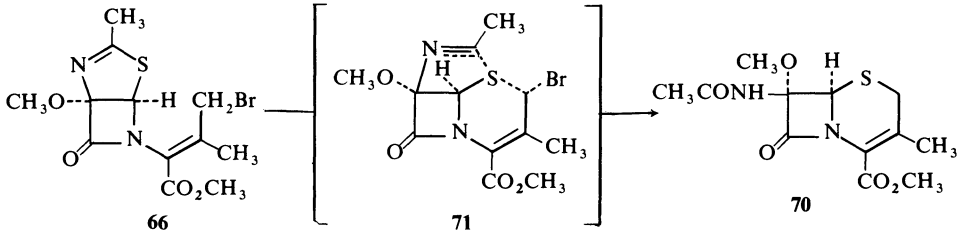
Following Cooper's method[4], the deconjugated ester with *natural* configuration **68** was subjected to *m*-chloroperbenzoic acid oxidation in the presence of a catalytic amount of trifluoroacetic acid in benzene to yield a complex mixture of products. After the entire product mixture was treated with phosphorous trichloride in methylene chloride, the products were separated by preparative t.l.c. on silica gel plates to give deacetoxy-7-methoxycephalosporin derivative **70**—oil; $\delta^{CDCl_3}_{p.p.m.}$, 2.15 (6H, broad s), 3.17 and 3.44

(1H + 1H, AB, J = 18 Hz), 3.86 (3H, s), 5.10 (1H, s) and 7.18 (1H, broad s); $\nu_{max}^{CH_2Cl_2}$, 1777, 1731 and 1705 cm^{-1}—in about 5 per cent yield and the 6-methoxypenicillin derivative **63**—oil; $\delta_{p.p.m.}^{CDCl_3}$, 1.46 (3H, s), 1.56 (3H, s), 2.11 (3H, s), 3.54 (3H, s), 3.82 (3H, s), 4.43 (1H, s), 5.63 (1H, s) and 7.30 (1H, broad s); $\nu_{max}^{CH_2Cl_2}$, 1780, 1755 and 1703 cm^{-1}—in about one per cent. The synthetic penicillin derivative **63** was identical with the authentic substance, synthesized from 6-aminopenicillanic acid **62** by Koppel's method[12] by comparison of n.m.r., i.r., t.l.c. and high-pressure chromatography. Also, the synthetic cephalosporin derivative **70** was identical with the authentic substance, synthesized from **63** by Morin's reaction[14] by comparison of n.m.r., i.r., t.l.c. and high-pressure chromatography.

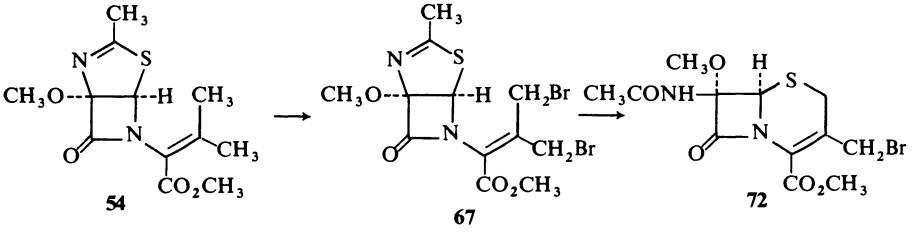


A more direct approach for converting the β-lactam thiazoline **54** to the cephem-ring system would be to utilize the allylic bromide **66** as follows. Since the sulphur atom is nicely located to reach the reactive centre of the allylic bromide system in **66**, a direct transformation of **66** to **70** could be expected via a transition state like **71**.

To study this possibility, the bromide **66** was separated from the bromide **65** by high-pressure chromatography, using corasil-I in ethyl acetate (one part) and hexane (12 parts) solvent system. The retention time of **66** was 15 min and that of **65** was 20 min. The ratio (**65**:**66**) of the monobromides was about 3:2. When the methylene chloride solution of the monobromide **66** was allowed to evaporate to dryness under atmospheric pressure and left to stand at room temperature for three days, the starting material completely disappeared and a new substance appeared. Isolation of the product by preparative t.l.c. on silica gel plates gave the desired deacetoxy-7-methoxycephalosporin derivative **70** in 40 per cent yield. To carry out this transformation efficiently the thickness of the evaporated film of the starting material is obviously important. Under the same conditions, the isomeric monobromide **65** was recovered unchanged. Incidentally, the isomeric monobromide **65** can also be converted to **70** through recycling back to the conjugated ester **54**, i.e. **65** → (**68** + **69**) → **54** → **66** + **65**.

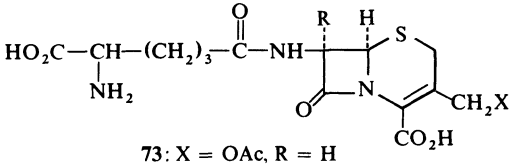


We can naturally imagine that the same type of cyclization reaction would be feasible on the dibromide **67**, which would be a better route to the 7-methoxycephalosporin ring system. The dibromide **67** was readily available by *N*-bromosuccinimide bromination of **54** in about 70 per cent yield. In our preliminary experiments, the dibromide **67** does go to the desired 3-bromomethyl-7-methoxycephalosporin derivative **72** under the same reaction condition as described before, but the yield is much lower than for the monobromide case, obviously because the desired product **72** decomposes slowly under these conditions.



54 **67** **72**

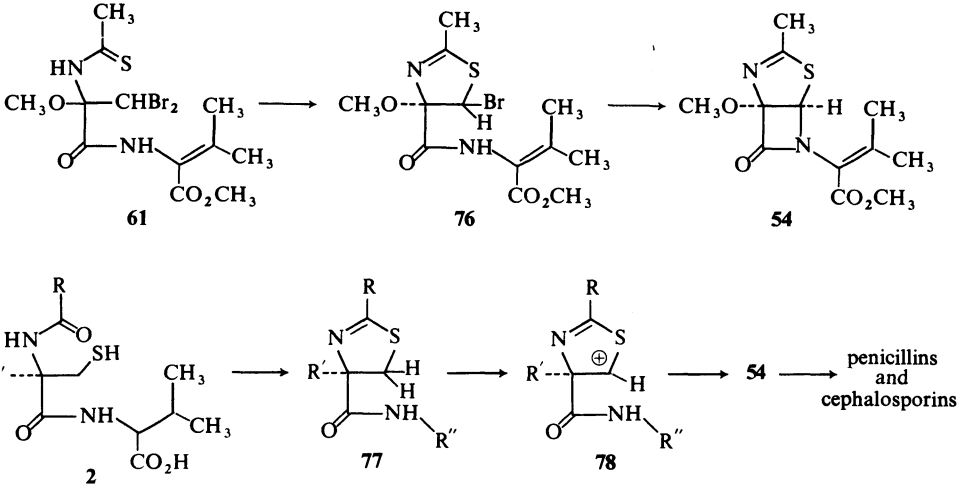
From the synthetic point of view, the deacetoxycephalosporin derivative **70** could be considered essentially equivalent to 7-methoxy-cephalosporin C derivative because Webber and his co-workers[15] have already established a procedure for converting deacetoxycephalosporin C **74** to cephalosporin C **73**. Furthermore, to our gratification, Fujisawa Pharmaceutical Co. in Osaka announced an isolation of deacetoxy-7-methoxy-cephalosporin C **75** from natural sources[16].



73: X = OAc, R = H
74: X = H, R = H
75: X = H, R = OCH_3

Although extensions, modifications, improvements and refinements are still required, completion of a synthesis of the bicyclic cephem- and penam-ring systems from the acyclic intermediate with control of stereochemistry would present one biogenetic-type solution for the synthesis of the penicillin–cephalosporin antibiotics, because the double cyclization reaction most likely proceeds through the intermediate **76** and a biogenetic scheme[17] involving an intermediate like **78**, which is equivalent to **76**, is proposed. Along this line, studies on oxidative cyclization of the compound **77** to **54** are in progress in our laboratories.

It is a great pleasure to acknowledge the collaboration of Dr Shin-ichi Nakatsuka who studied the crucial double cyclization reaction, and Dr Hideo Tanino, who prepared the authentic β-lactam thiazoline and studied the transformation of the β-lactam thiazoline to the cephem- and penam-ring systems.



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