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Straightforward Synthesis of 7<latex>α</latex>-Methoxy-1-Oxacephems from Penicillins

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Straightforward synthesis of 7α-methoxy-1-oxacephems from penicillins†

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A straightforward and industrially feasible synthesis of 7β-acylamino-7α-methoxy-3-[(1-methyl-1*H*-tetrazol-5-ylthio)methyl]-1-oxa-3-cephem-4-carboxylic acid (**35**) from penicillins is described. Reaction of 6α-acylaminopenicillanate *S*-oxides with triphenylphosphine gave epioxazolines (**16**) which were transformed into allylic alcohols (**28**) via allylic chlorides (**22**) and iodides (**27**). Intramolecular etherification of **28** gave 7α-acylamino-3-exomethylene-1-oxacepham-4α-carboxylate (**30**), a versatile key intermediate. 7α-Methoxylation of **30**, followed by substitution with sodium 1-methyl-1*H*-tetrazol-5-ylthiolate at C_3 and side chain cleavage, afforded the methoxyamine (**33**), the desired 1-oxa-3-cephem nucleus, which on acylation and subsequent deprotection gave **35** (6059-S free acid, where the acyl is *p*-hydroxyphenylmalonyl).

Recently, much interest has been focused on nuclear analogues of β-lactam antibiotics, since some of these compounds, including both naturally occurring and synthetic varieties, have shown enhanced or unique antibacterial activity. In regard to the 1-oxacephem analogues, compounds **1** (Sheehan & Dadíc 1968) and **2** (Wolfe *et al.* 1974) with this type of ring system had already been prepared by 1974. However, interest seems to have evolved only since 1974 when Christensen and his collaborators (Cama & Christensen 1974; Firestone *et al.* 1977) of the Merck Company showed for the first time that 1-oxacephalothin (**3**) had antibacterial activity comparable with that of cephalothin. Subsequently, Nayler of the Beecham company reported the preparation of the optically active 1-oxacephem-4-carboxylic acid (**4**) (Brain *et al.* 1977). We also started synthetic studies on this new class of compounds in the hope that some clinically useful ones could be discovered. During the period from 1975 to 1977, we prepared a large number of the 1-oxacephem derivatives depicted by the general formula **5**, and discovered a biologically very interesting compound (**6**), which we called 6059-S (Narisada & Nagata 1977; Yoshida *et al.* 1978). This compound is now under clinical evaluation.

We have already developed three routes to 1-oxacephems (Hamashima *et al.* 1978; Narisada *et al.* 1977) as shown in chart 2. In each route, the O–C–C–C fragment necessary for constitution of the future 1, 2, 3 and 3′ part of the 1-oxacephem (**11**) was supplied from the outside of the molecule of the azetidinone intermediate (**7**, **8** or **9**). This elaboration should be followed by elimination of the three-carbon moiety of the 3-methyl-butenoate side chain to give the common phosphorane intermediate (**10**) and to the 1-oxacephem (**11**). Such synthetic elaborations necessitated a multi-step synthesis which involved the repetitive steps of supplying and removing three carbons and resulted in a very low overall yield of the final product.

In our strategy for a new synthesis, we planned to utilize the three-carbon moiety of the 3-methyl-butenoate chain for the future C_2–C_3–$C_{3'}$ part of the 1-oxacephem nucleus (**11**) and also to secure the 3-exomethylene-1-oxacepham (**13**) as a versatile intermediate, since its conversion into 3-methyl, 3-functionalized methyl or 3′-nor-1-oxacephems might be easy. Thus, the key in the new synthesis was the preparation of compound **12**.

† Synthetic studies on β-lactam antibiotics, part 14. For part 13, see Hamashima *et al.* (1979).

The known 6-*epi*-penicillin ester *S*-oxides (**15**) prepared from penicillins or 6-APA (**14**) in 70–80% yields were heated with phosphorus derivatives, such as triphenyl phosphine and trialkyl phosphite, giving the *epi*-oxazoline-azetidinone (**16**) in good yields. When benzhydryl 6-*epi*-benzoylamidopenicillanate β-*S*-oxide (R^1 = Ph, R^2 = Ph_2CH; m.p. 161–163 °C (dec.)) and triphenyl phosphine were used as substrate and reagent, respectively, we obtained **16** (R^1 = Ph, R^2 = $CHPh_2$, m.p. 115–117 °C, $[\alpha]_D^{22} = -32.3 \pm 0.7°$ ($CHCl_3$, c = 1.02)) in 80% yield. The compounds **15** with other acyl (R^1 = $PhCH_2$, $PhOCH_2$) and ester groups (R^2 = CH_2Ph, *t*-Bu) reacted similarly to give the corresponding *epi*-oxazolines **16**. As I have not enough time to discuss properly all acyl and ester derivatives, I shall use only the benzoyl and benzhydryl derivatives as representative compounds for later discussion.

Now, formation of the *epi*-oxazoline (**16**) markedly contrasts with the exclusive formation of the thiazoline (**18**) in a similar reaction of the normal penicillin ester *S*-oxide (**17**) (Cooper &

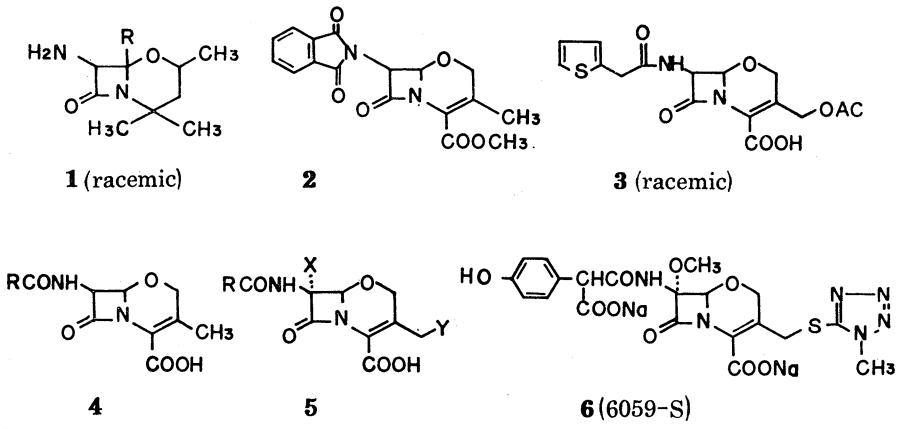

CHART 1

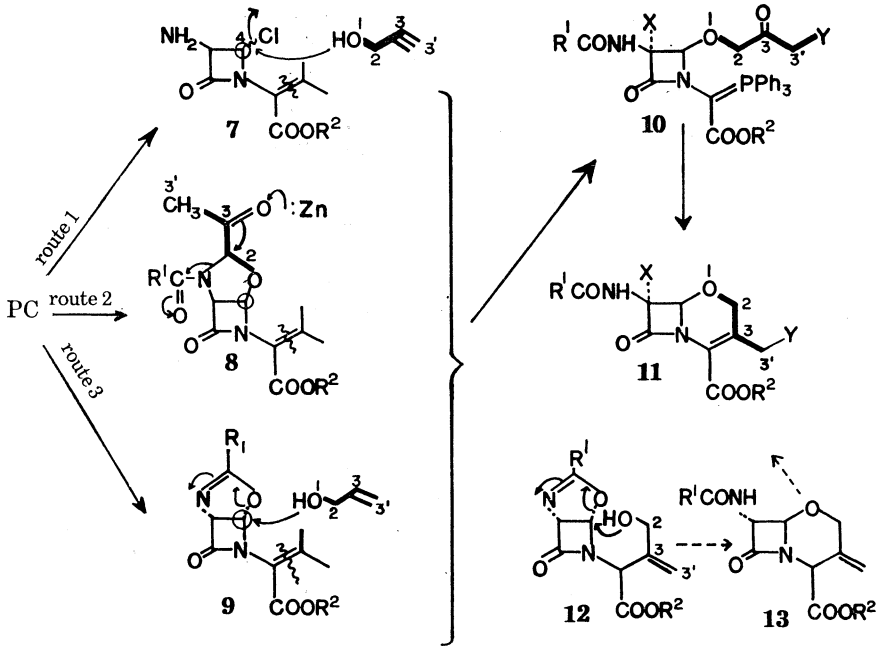

CHART 2

José 1970; Hatfield *et al.* 1970). Probably, removal of triphenylphosphine sulphide is assisted by the attack of the amide carbonyl from the opposite side as depicted in **20**.

Our next objective was to oxidize this *epi*-oxazoline (**16**) at the allylic methyl to form the allylic alcohol. Unfortunately, however, every attempt was unsuccessful. We therefore examined allylic halogenation. Luckily, we found that allylic chlorination proceeded well by simple addition of chlorine or sulphuryl chloride to give the dichloride (**21**) as the primary product, which on treatment with aqueous sodium bicarbonate gave the allylic chloride (**22**) (R^1 = Ph, R^2 = $CHPh_2$, m.p. 102–104 °C) in 75–80 % yield. The assumption that an ene-type reaction as depicted in **23** operated in this reaction was supported by an experiment with the use of the

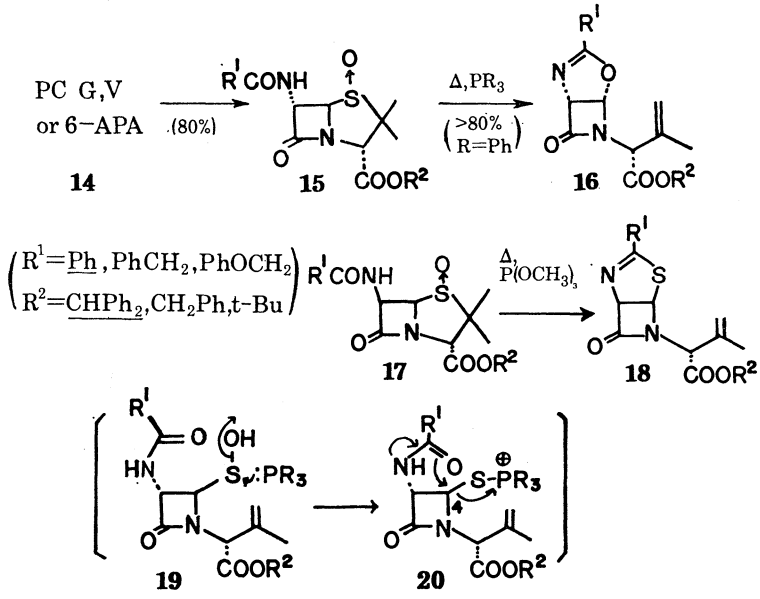

CHART 3

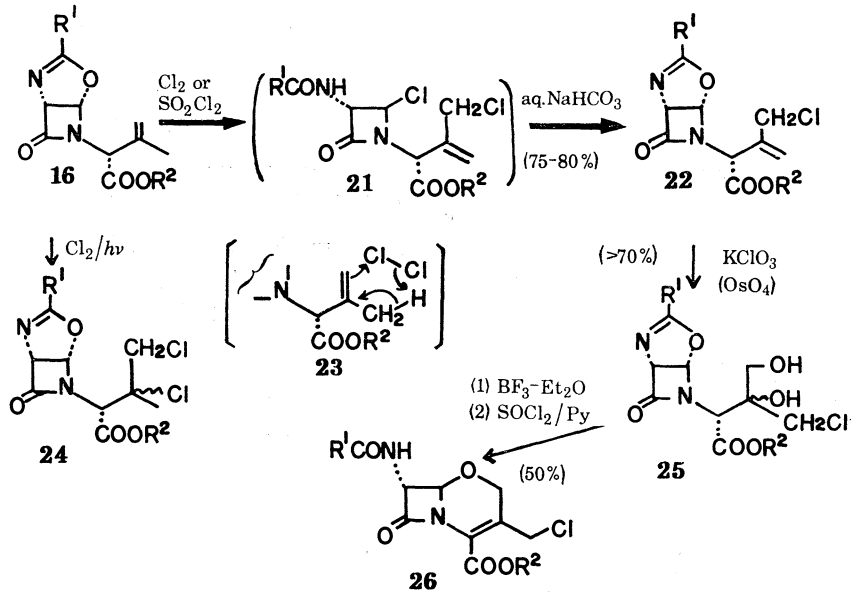

CHART 4

deuterated analogue of **16**. Interestingly, chlorine addition occurred smoothly under irradiation giving the dichloride (**24**). Now, the chlorine atom in the allylic chloride (**22**) was found to be poorly reactive and every attempt to convert **22** directly into the allylic alcohol failed. The terminal double bond was also poorly reactive owing to its electron-deficient nature, but its glycolation was effected by oxidation with potassium chlorate in the presence of a catalytic amount of osmium tetroxide giving a mixture of the two stereoisomeric glycols (**25**) in more than 70 % yield. Although cyclization took place smoothly with boron trifluoride, subsequent dehydration to obtain the 1-oxa-3-cephem (**26**) (R^1 = Ph, R^2 = $CHPh_2$, m.p. 132–134 °C (dec.)) proceeded rather poorly. We obtained **26** in only 50 % yield.

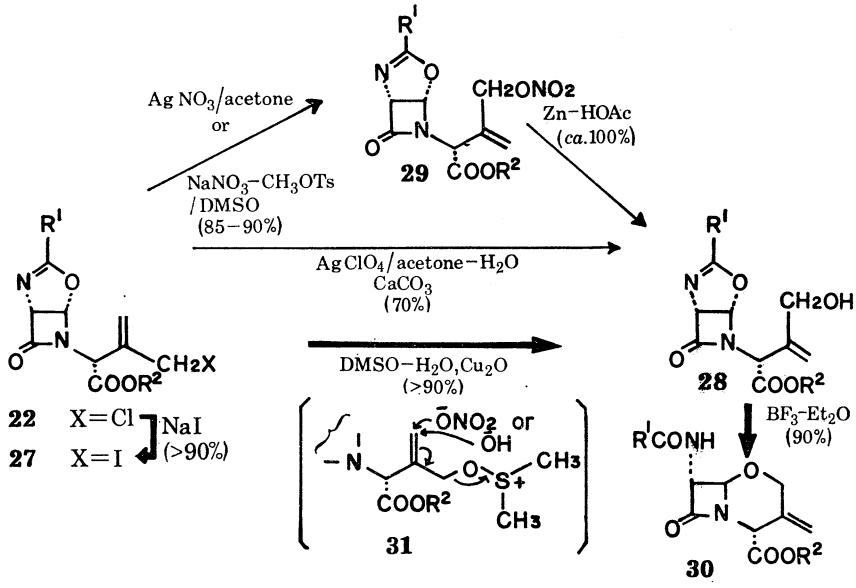

CHART 5

In search of other efficient routes, we next converted the chloride (**22**) into the reactive iodide (**27**) (R^1 = Ph, R^2 = $CHPh_2$, m.p. 90–92 °C) in high yield by the conventional manner. This compound was found to be reactive as expected, giving in good yield the allylic alcohol (**28**) (R^1 = Ph, R^2 = $CHPh_2$, m.p. 103–105 °C) on reaction with silver perchlorate in aqueous acetone in the presence of calcium carbonate. Alternatively, reaction of **27** with silver nitrate in acetone or a combination of sodium nitrate and methyl *p*-toluenesulphonate in dimethyl sulphoxide gave the nicely crystalline nitrate (**29**) (R^1 = Ph, R^2 = $CHPh_2$, m.p. 128–133 °C) in 85–90 % yield in either case. The use of methyl *p*-toluenesulphonate as a trapping agent of the iodide ion was critical in the latter reagent. The nitrate (**29**) was reduced with zinc and acetic acid quantitatively to the allylic alcohol (**28**). Thus, the reactions with the use of silver salts did proceed cleanly to give the allylic alcohol, but the use of such reagents is not suitable for industrial production. In an alternative transformation, **27** was warmed slightly in aqueous dimethyl sulphoxide in the presence of cuprous oxide, to give the allylic alcohol (**28**) in more than 90 % yield. Obviously, because of its simplicity, this transformation is superior to the two-step conversion via the nitrate intermediate (**29**) with the use of sodium nitrate and methyl *p*-toluenesulphonate reagents. We suggest the intermediacy of the sulphonium ion (**31**) in these reactions; this ion eliminates dimethyl sulphoxide on attack of either the nitrate or

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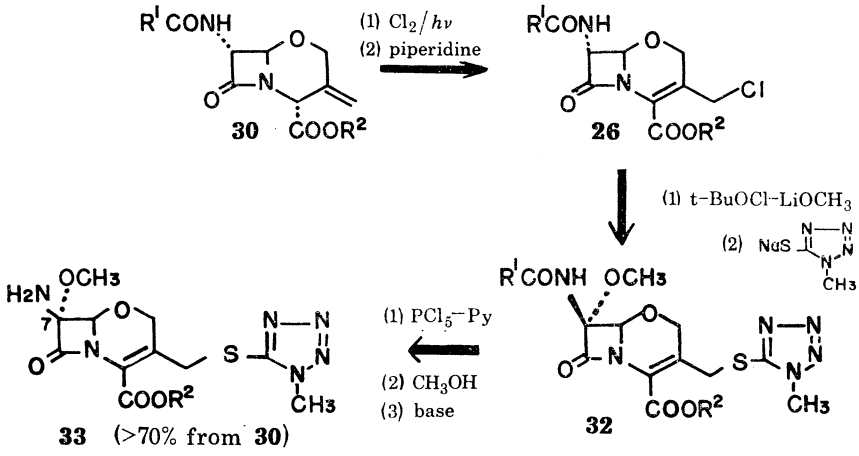
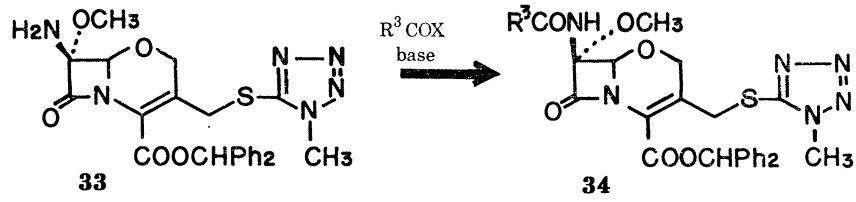
the hydroxyl ion to give **29** or **28**. The allylic alcohol (**28**) was cyclized with boron trifluoride to the desired 3-exomethylene-1-oxacepham-4-carboxylate (**30**) (R^1 = Ph, R^2 = $CHPh_2$, m.p. 167–169.5 °C, $[\alpha]_D^{22.0} = -42.1 \pm 0.8°$ ($CHCl_3$, c = 1.06)) in high yield.

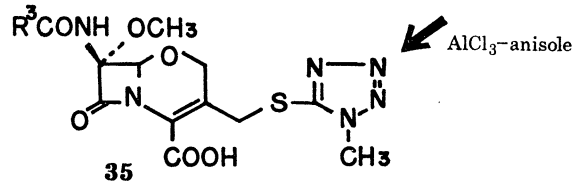


33 (>70% from **30**) **32**

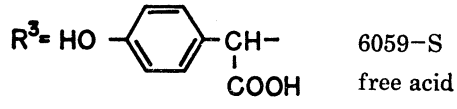
CHART 6



33 **34**



35



6059–S free acid

CHART 7

Having the versatile key intermediate **30** on hand, we further investigated its transformation into the 7α-methoxy-1-oxacephem nucleus (**33**) and the results are shown in chart 6. Addition of chlorine to the exomethylene double bond in **30** was effected by irradiation and subsequent treatment with piperidine gave the 3-chloromethyl-1-oxacephem (**26**). This compound was methoxylated at the 7α-position by reaction with *tert*-butylhypochlorite and lithium methoxide at low temperature, and subsequent substitution with sodium 1-methyl-tetrazolyl mercaptide, gave the 7α-methoxy-7β-benzoylamino-1-oxacephem-4-carboxylate (**32**) (R^2 = $CHPh_2$, crystals having benzene of crystallization, m.p. 88–89 °C) which underwent the conventional side chain cleavage to give the desired methoxyamine (**33**) (R^2 = $CHPh_2$, m.p. 170–171.5 °C, $[\alpha]_D^{23.5} = -204 \pm 4.7°$ ($CHCl_3$, c = 0.50)) as crystals in more than 70% yield from the exomethylene intermediate (**30**). It should be emphasized that unlike the corresponding cephalosporin,

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almost no epimerization at the 7-position took place in this cleavage reaction. This fact enabled us to introduce the 7α-methoxy group before modification of the side chain necessary for exhibition of antibacterial activity.

A variety of 7α-methoxy-1-oxacephem derivatives (**35**) were prepared by applying conventional acylation methods used in the cephalosporin series to the methoxy amine (**33**) and subsequent deprotection of the resulting 7β-acylaminobenzhydryl ester (**34**) with aluminium trichloride and anisole. This deprotection technique developed recently in our laboratories was found to be superior to the known trifluoroacetic acid–anisole method in every respect (Tsuji *et al.* 1979).

In this way, we established a straightforward and industrially feasible synthetic route to the 7α-methoxy-1-oxacephem nucleus starting from penicillins.

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