Pergamon

Bioorganic & Medicinal Chemistry, Vol. 3, No. 9, pp. 1157–1181, 1995

0968-0896/95 $29.00 + .00

0968-0896(95)00088-7

REVIEW ARTICLE

Cycloaddition and Related Reactions of Cephalosporin Antibiotics

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Contents

1. Introduction

Cephalosporins are among the most important antibiotics.[1,2] In an effort to obtain derivatives possessing a broader antibacterial spectrum, greater stability towards β-lactamases and improved pharmacological properties, modifications of the cephem basic skeleton have been carried out.[1–5] Cycloaddition reactions are useful, highly selective methods for the synthesis of cephalosporins containing a modified cephem nucleus (Fig. 1). Many of these derivatives are either unobtainable by other synthetic methods or can only be prepared with much difficulty.

In this paper the efforts of our laboratory are summarized and related work on cycloaddition reactions of cephalosporins carried out in the last 20 years are described.

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Abbreviations: G = $PhCH_2CO$-; V = $PhOCH_2CO$-; TCE = Cl_3CCH_2-; Ts = *p*-CH_3-C_6H_4-SO_2-; PMB = *p*-CH_3O-C_6H_4-CH_2-; Allyl = CH_2=CH-CH_2-; PNB = *p*-NO_2-C_6H_4-CH_2-; Pht = phthalyl; Tr = Ph_3C-; tBu = Me_3C-; TMS = Me_3Si-; Bn = C_6H_5-CH_2-; DAA = D-α-aminoadipoyl-; Th = 2-(C_4H_3)-CH_2O-; BOC = tBuOCO-; BH = Ph_2CH-; MT = 4-methyl-1,3-thiazol-2-yl-; PG = $PhCH(NH_2)CO$-; ATMO = (2-aminothiazol-2-yl)-2-oximinoacetyl- (or its protected derivative).

2. Modifications at C-2

2.1. *2-Spiro derivatives*

The starting material 2-alkenylcephalosporins are prepared mainly by three methods: 1) ring expansion of penicillins;[6–8] 2) addition-elimination processes;[9,10] 3) Mannich reactions of cephalosporin sulphoxides or sulphones with aldehydes (or paraformaldehyde) in the presence of primary or secondary amine salts[11–13] or by using bis-(*N,N*-dimethylamino)methane.[14,15]

In order to study the 1,3-dipolar cycloaddition reactions of 2-methylenecephalosporins we have prepared a variety of cephems with different S-1, C-3, C-4 and C-7 substituents. We used the Mannich reaction approach of Wright[11] or our improved non-aqueous method (Fig. 2, Table 1).[16,19]

In a preliminary experiment a 2-methylenecephalosporin (**18**) was reacted with diazomethane and diphenyldiazomethane (Fig. 3).[20] Treatment with diazomethane

at 0 °C for 5 min gave two products which decomposed upon standing at room temperature or during chromatography. A spirocyclopropylcephem (**19**) was isolated resulting from the isomeric mixture of 2-spiro-pyrazolidinocephems (**21**). When **18** was treated with diphenyldiazomethane the reaction was complete after 30 min at room temperature and an isomeric mix-ture of two cyclopropanes (**20**) was isolated.

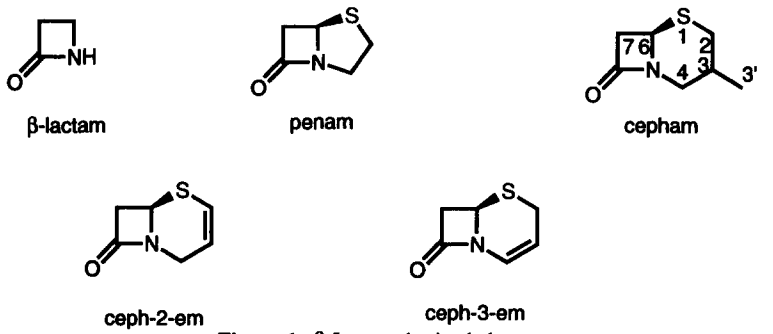


Figure 1. β-Lactam basic skeletons.

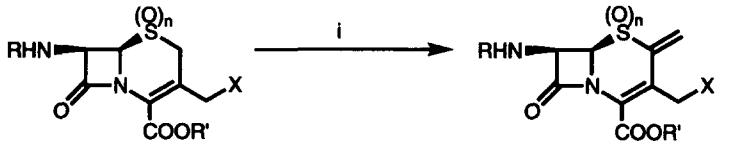


Figure 2. Mannich reactions of cephalosporins.
Reagents: Method A: i) CH_2O, Et_2NH·HCl, tBuOH, $CHCl_3$, reflux, 24 h; Method B: i) *p*-CH_2O, Et_2NH·HCl, tBuOH, $CHCl_3$, reflux, 24 h; Method C: i) method A, then PBr_3, DMF, 0 °C, 30 min; Method D: Method B, then AcCl, KI, DMF, 0 °C, 2 h.

Table 1. Synthesis of 2-methylenecephalosporins

Starting material	R	R'	X	*n*	product	method	yield (%)
1	$ClCH_2CO$	CH_3	H	1	**8**	A	89
2	$ClCH_2CO$	$CHPh_2$	H	1	**9**	A	78.5
-	$ClCH_2CO$	$CHPh_2$	H	0	**10**	C	20.7
3	$ClCH_2CO$	$CHPh_2$	OAc	1	**11**	B	69.5
-	$ClCH_2CO$	$CHPh_2$	OAc	0	**12**	D	32.3
4	$ClCH_2CO$	CH_3	S-tetr.*	1	**13**	A	74.2
5	Th†	$CHPh_2$	OAc	1	**14**	B	57.2
6	$PhCH_2CO$	CH_3	OAc	1	**15**	A	79.3
-	$PhCH_2CO$	CH_3	OAc	0	**16**	D	43.5
7	$PhCH_2CO$	CH_2CCl_3	H	2	**17**	B	81.4

*S-tetr. = (1-methyltetrazol-5-yl)thio-.
†Th = 2-thienylacetyl-.

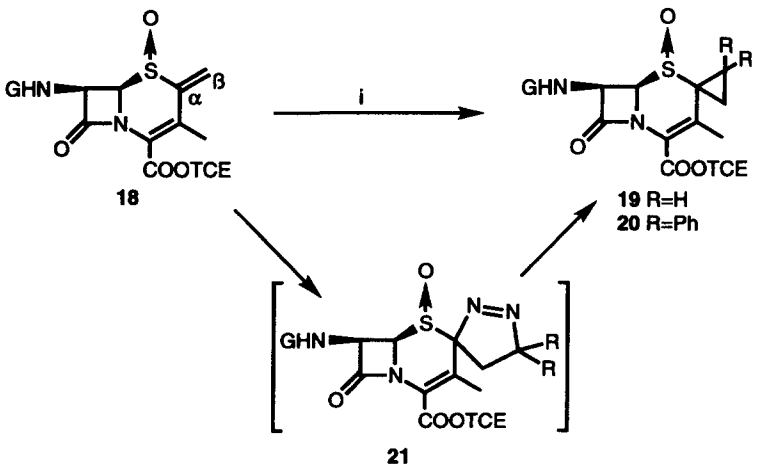


Figure 3. 1,3-Dipolar cycloaddition reaction of trichloroacetyl 2-methylene-7-β-phenylacetamidocephalosporanate 1*S*(β)-oxide with diazoalkanes. Reagents: i) N_2CR_2, CH_2Cl_2, 0 °C, 5 min (R = H) or 30 min (R = Ph).

In order to obtain further insight into the nature, stereochemical outcome and the effects of substituents on the 1,3-dipolar cycloaddition reaction, we subjected a range of 2-methylenecephalosporins (**8–17**) to several diazoalkanes (diazomethane, phenyldiazomethane, diphenyldiazomethane and ethyl diazoacetate) (Fig. 4, Table 2) at 5 °C in dichloromethane.[16–19,21,22] The observed reaction times (determined by TLC) are also listed in Table 2. The 1-pyrazolines (on the basis of FMO considerations;[23] β-adducts[24] of type **21**) initially formed by cycloaddition underwent spontaneous decomposition to give the spirocyclopropanes **22–34**.

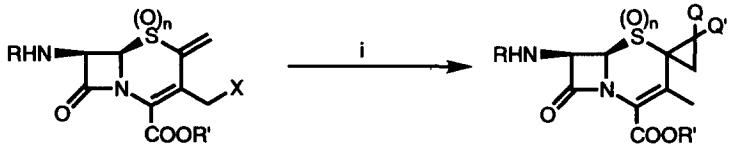
The reaction of 2-methylenecephalosporins with diazomethane yielded two compounds, which underwent decomposition (after purification/solvent removal) to give single products (**24, 25, 32** and **33**). Reactions with diphenyldiazomethane provided two derivatives: a major product [**22, 26, 28, 30** and **31(major)**] and a minor [**22, 26, 30** and **31(minor)**] in a ratio between 3:1 and 9:1. In the case of 2-methylenecephalosporin sulphide (**12**) the minor product could not be detected. Cycloaddition with phenyldiazomethane and ethyl diazoacetate led to three compounds in differing amounts. The minor components were unstable or inseparable thus their C-2,C-2' configurations were not determined. Sulphide **12** did not react with ethyl diazoacetate. The configurations of the new stereocentres of the spirocephems and their configurations were unambiguously determined by ^1H-{^1H} NOE experiments and molecular modelling (Alchemy II). It was found that the major products have the 2*R-exo* (open) configuration, whereas the minor products possess the 2*S-exo* (open) structure. The minor product, **30(minor)**, bearing (1-methyltetrazol-5-yl)thiomethyl substituent at C-3 has a closed conformation due to the steric hindrance of the C-3 side chain. A radical mechanism[25] to account for their formation was also proposed.

Taking the reaction times into consideration we concluded: 1) substituents at C-3, C-4 and C-7 do not exert a significant effect on the reactivity of the 2-*exo* double bond; 2) the reduction of the sulphoxides to sulphides has a strong inactivating influence; 3) substituted diazoalkanes react more slowly (or not at all) with 2-methylenecephems.

In order to provide an explanation for these findings theoretical calculations were carried out on model systems of the dihydrothiazine ring of compound **8** (n = 1 and n = 0).[22] The results reveal that the LUMO energy of the sulphoxide is lower in any case than that of the sulphide, i.e. the value of $E_{HOMO\text{-}dipole} - E_{LUMO\text{-}sulphoxide}$ is always smaller. Hence, the reaction of diazomethane with 2-methylenecephalosporin sulphoxides is preferrable to that with 2-methylenecephalosporin sulphides. The difference is even more pronounced in reactions with less active substituted diazoalkanes.

The 2-methylenecephalosporins did not react with phenylazide, cyclopentadiene, 2,3-dimethylbutadiene and Danishefsky's diene even upon prolonged heating or in the presence of Lewis acid catalysts.

Soon after our first publications appeared excellent work was published by the Merck[26] and other[27–30] groups on 2-methylene-, (unstable) 2-spiropyrazoline- and 2-spirocyclopropyl-7-α-methoxycephalosporin sulphones obtained by the 1,3-dipolar cycloaddition approach. Several were found to be potent inhibitors of human leukocyte elastase (Fig. 5).



8-17 **22-34**

Figure 4. Synthesis of 2-spirocyclopropylcephalosporins **22–34**. Reagents: i) $QQ'CN_2$, CH_2Cl_2, 5 °C (for the reaction times see Table 2).

Table 2. Reactions of 2-methylenecephalosporins with diazoalkanes

starting material	reagent	reaction time (h)	yield (%)	products (ratio)
8	Ph_2CN_2	0.5	26.7/6.7	**22** (8:1)
8	$PhHCN_2$	0.4	52.4	**23**
8	H_2CN_2	0.15	43.3	**24**
10	H_2CN_2	2	38.8	**25**
11	Ph_2CN_2	0.5	52.1/12.3	**26** (8:1)
11	$PhHCN_2$	0.5	54	**27**
12	Ph_2CN_2	48	46.2	**28**
12	$(EtO_2C)_2HCN_2$	-	-	**29**
13	Ph_2CN_2	0.3	59.7/6.5	**30** (9:1)
14	Ph_2CN_2	0.5	46.9/16.8	**31** (3:1)
16	H_2CN_2	2	68	**32**
17	H_2CN_2	0.15	58.4	**33**
17	$(EtO_2C)_2HCN_2$	1	70.5	**34**

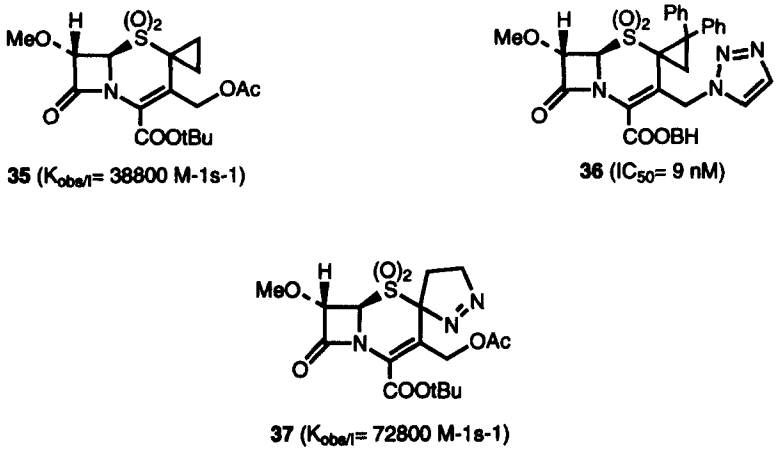


Figure 5. 2-Spirocephalosporins possessing HLE inhibitory activity.

Structurally analogous 2-spirocyclopropyl-, 2-spiroaziridine- and 2-spiroepoxycephems were prepared by Spry using a different approach.[31-33] However, they did not display significant antibacterial activity (no data given).

2.2. *Cephalosporin C-2 dipoles*

Cephalosporin C-2 azides were prepared[34] and their reactions were studied by Hoshide *et al.*[35] When **38** (Fig. 6) was reacted with acetylene carboxylic acids, 2-(2-triazolo)cephalosporins (**39, 40**) were formed. When **38** was heated in carbon tetrachloride a ring expansion occurred providing **41**, probably via a nitrene intermediate. In contrast, when the ceph-2-em isomer **42** was refluxed in benzene, a penicillin derivative (**43**) formed by ring contraction.

Recently, an alternative approach was attempted by Lunn and Hipskind.[36] They aimed to convert cephalosporin sulphone **44** (Fig. 7) to carbacephems. They prepared the C-2 oxime (**46**) and tosylhydrazone (**49**) derivatives, ideal precursors of nitrile oxides and diazoalkanes. However, they were not stable and rearranged to monocyclic azetidinones (**48, 50**) probably via a tricyclic intermediate **47**.

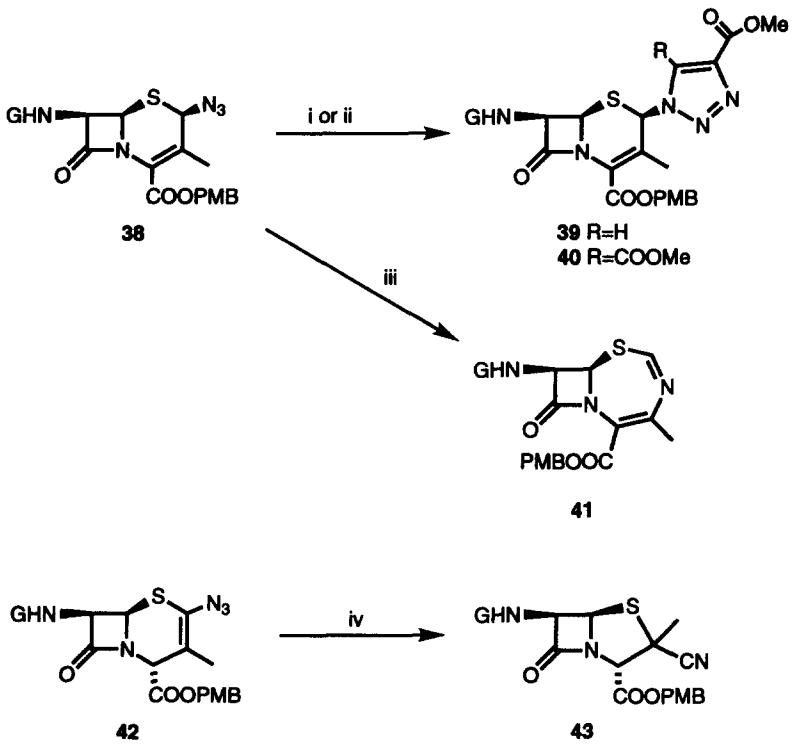


Figure 6. Reactions of 2-azidocephalosporins with acetylenes. Reagents: i) HC≡C-COOMe; ii) MeOOC-C≡C-COOMe; iii) reflux, CCl_4, 21%; iv) reflux, C_6H_2, 11%.

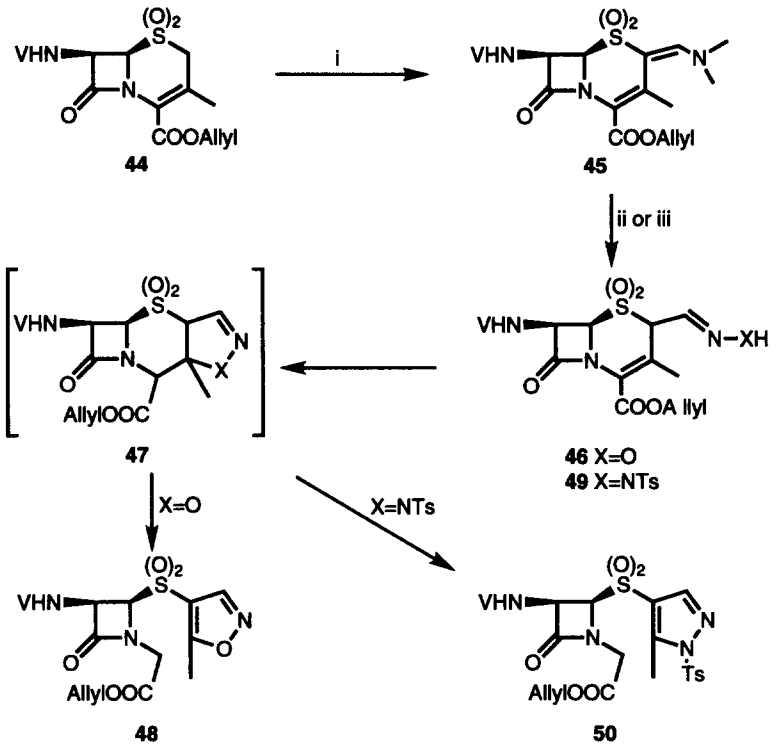


Figure 7. Rearrangements of cephalosporin 2-oximes and tosylhydrazones. Reagents: i) $Me_2N{=}CH{-}Cl^+\ Cl^-$, pyr., MeCN; ii) H_2N-OH·HCl, TFA, MeCN; iii) H_2N-NHTs, TFA, MeCN.

3. Fused Derivatives

3.1. *Syntheses from monocyclic intermediates*

Fused cephalosporins are usually obtained by intramolecular 1,3-dipolar cycloaddition reactions.

When the sulphenium chloride **51** was reacted with excess diazomethane, a complex reaction mixture formed (Fig. 8).[37] The postulated intermediate diazosulphoxide **52** was considerably more reactive than a diazoketone adding to the double bond at low temperature without the use of a Lewis acid catalyst. The initially formed 2,3-pyrazolines were extremely unstable and an isomeric mixture of 2,3-cyclopropylcephalosporins (**53**) was obtained. This was converted to the free acids and reacylated with phenylacetyl chloride; the products displayed antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Sarcia lutea, Proteus vulgaris,* and *Escherichia coli* at 2 mg mL^{-1} concentration.

In an alternative approach, pioneered by Pearson, azacephalosporins were obtained. The monocyclic β-lactam **54** (Fig. 9)[38] was reacted with a bromoacetic acid ester and subsequently the thiomethyl group was transformed to the azide **55**. An acetylene function was incorporated by removal of one of the acidic hydrogens. When **56** was heated in toluene, a smooth intramolecular cycloaddition occurred to give the triazole **58**. The ceph-3-em double bond was introduced by a phenylselenylbromide addition → oxidation → spontaneous elimination reaction sequence. Triazole **60** was

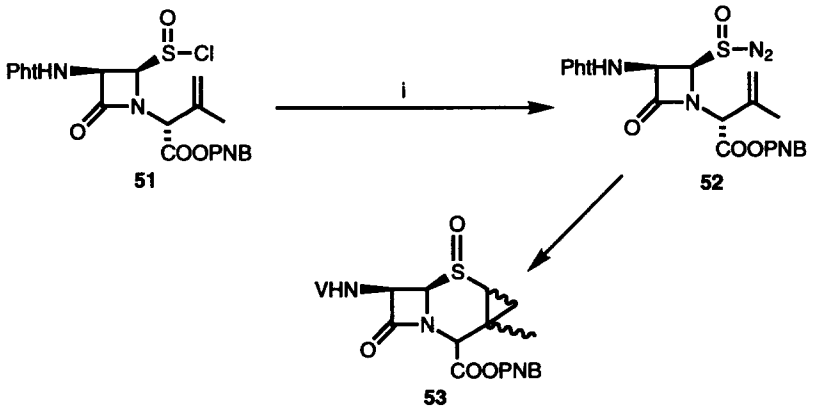


Figure 8. Synthesis of 2,3-cyclopropylcephalosporins. Reagents: i) 2.2 eq. N_2CH_2, 2 h 0–5 °C then 2 h 25 °C, 34%.

then converted to the corresponding phenoxyacetyl derivative which showed varying degrees of antibacterial activity [MIC values: 0.5 μg mL^{-1} against β-haemolytic *Streptococcus*; 2.5 μg mL^{-1} against *S. aureus* (Oxford); 5 μg mL^{-1} against *S. aureus* (Russell, penicillinase producer); <0.2 μg mL^{-1} against *B. subtilis*].

A different approach led to an isomeric tricyclic aza-1-dethiacephalosporin (Fig. 10).[39] The acetylene-β-lactam **62**, prepared via a [2+2] cycloaddition reaction, was transformed to the azide **65** in several steps. Reflux in benzene gave rise to the desired tricyclic 2-aza-1-dethiacephem (**66**). The free carboxylic acid showed only poor antibacterial activity (no data given).

A similar reaction sequence was used by Nagakura (Fig. 11).[40] The allylazetidin-2-one (**67**) was reacted with benzyl glyoxylate. The secondary alcohol **68** was transformed to the azide **69** upon treatment with sodium azide and subsequent heating in toluene for 8 h provided the unstable intermediate tricyclic derivative which rearranged to a 3-aza-1-dethiacephem (**70**).

A similar rearrangement was observed later by Murthy.[41]

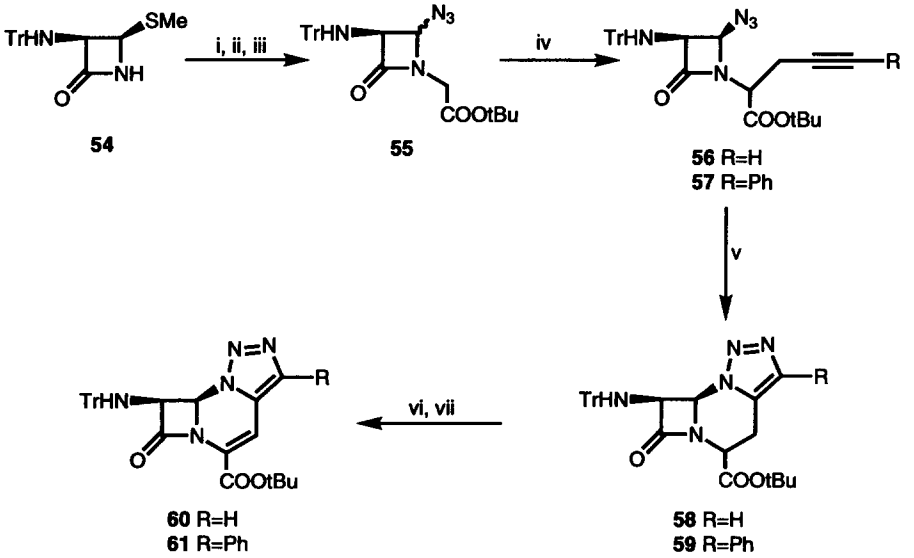


Figure 9. Synthesis of tricyclic 1-aza-1-dethiacephalosporins. Reagents: i) $BrCH_2COOtBu$, K_2CO_3, DMF; ii) Cl_2, CCl_4; iii) NaN_3, DMF, then chromatography; iv) HMDS, THF, nBuLi, $BrCH_2$-C≡CR (R = H, Ph); v) toluene, reflux, 8 h, 86%; vi) HMDS, THF, PhSeBr; vii) mCPBA, EtOAc.

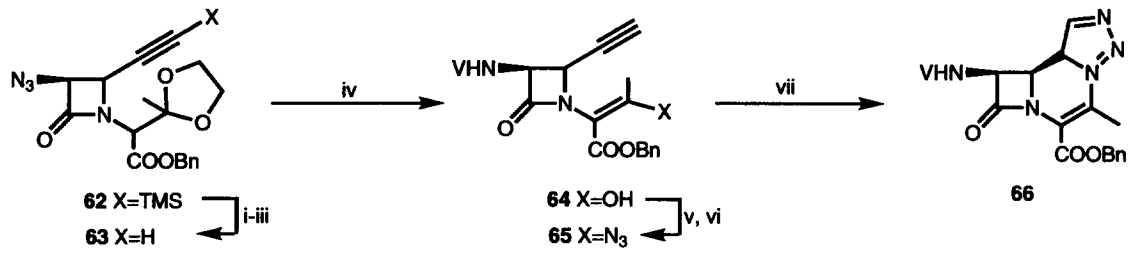


Figure 10. Synthesis of tricyclic 2-aza-1-dethiacephalosporins. Reagents: i) Et_4NF, THF; ii) H_2; iii) VCl; iv) TFA; v) MsCl; vi) NaN_3; vii) C_6H_6, reflux, 15 min, 42%.

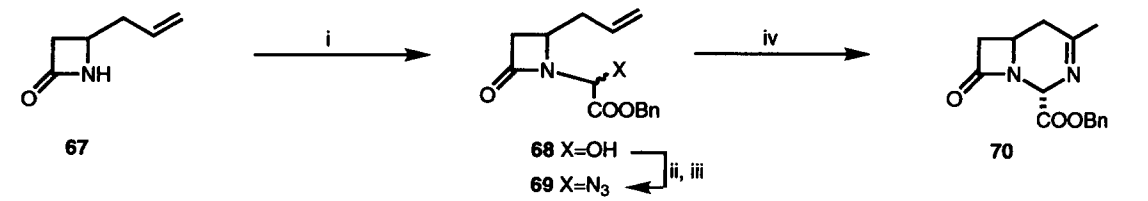


Figure 11. Synthesis of 3-azacephems. Reagents: i) O=CH-COOBn, C_6H_6, reflux, 6 h; ii) MsCl, TEA, CH_2Cl_2, 0 °C, 15 min; iii) NaN_3, glyme and H_2O, 0 °C, 15 min; iv) toluene, reflux, 8 h, 31%.

3.2. *Syntheses from cephalosporin precursors*

A 3,4-fused cephalosporin (**73**) (Fig. 12) was obtained by 1,3-dipolar cycloaddition reactions of diazomethane on the ceph-3-em double bond.[42] The reaction was complete after 2 days giving the 2-pyrazoline **73**.

When the reaction was re-examined in our laboratory[43-46] Farkas found that the ceph-3-em bond reacts with diazomethane in a completely regio- and stereoselective fashion. Formation of 1-pyrazoline **75** occurred (Fig. 13) when the reaction was carried out in dichloromethane-ether at room temperature for 7 days. However, in dimethylformamide 2-pyrazolines of type **73** formed. The structures of the cycloadducts were unambiguously confirmed by NMR and X-ray crystallography.[45,46] The Δ^3 double bond was found to be unreactive towards substituted diazoalkanes. The decarboxylated derivative **74d** did not undergo cycloaddition reaction.

In contrast, Ozawa *et al.* have reported successful reactions between cephems and diphenyldiazomethane which gave 3,4-cyclopropylcephams.[47,48]

For radical clock experiments in penicillin–cephalosporin biosynthesis 3,4-cyclopropylcephems (e.g. **76**) were also synthesized.[49]

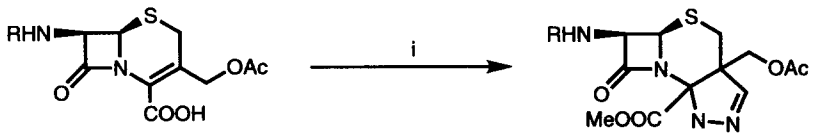
One of the key steps in penicillin–cephalosporin biosynthesis is the ring expansion of penicillin N (**77**) to deacetoxycephalosporin C (**81**) by an enzyme deacetoxycephalosporin C/deacetylcephalosporin C synthase (DAOC/DACS).[50] The reaction is thought to involve radical intermediates (**78–80**) (Fig. 14). As a probe for carbon free radicals the cyclopropylbinyl test was selected (Fig. 15).[51] Cyclopropylcarbinyl radicals (**82**) rapidly rearrange to homoallyl radicals (**83**). Therefore molecules, where such radicals would be generated by the proposed reaction mechanism might act as radical clocks. The time scale of this rearrangement is such that it was hoped that formation of a cyclopropylcarbinyl radical in a substrate such as **76** would lead to ring opening relatively quickly with respect to radical trapping.

In model experiments[80] compound **84** (Fig. 16) was N-protected with benzyl chloroformate and subsequently oxidized with 3-chloroperoxybenzoic acid in dichloromethane to give the sulphoxide **86**. Direct cyclopropanation of **86** using $CH_2N_2/Pd(OAc)_2$ was not successful. 1,3-Dipolar cycloaddition with diazomethane was, therefore, undertaken (7 days, 5 °C) providing the 3,4-pyrazoline **87**. Surprisingly, under the reaction conditions the PNB ester was not stable and partial trans-esterification to the methyl ester (**88**) was also observed. Both pyrazolines were relatively stable to heat. Nitrogen elimination providing cyclopropanes **89** and **90** occurred only after 8 h reflux in xylene. Reduction (AcCl/KI), catalytic hydrogenation and HPLC purification led to the 3,4-cyclopropylcepham nucleus **93**.

The C-3,C-4-configuration of the cyclopropane derivatives was defined as 3*R*,4*R* (i.e. β-cyclopropane ring) by NOE experiments.

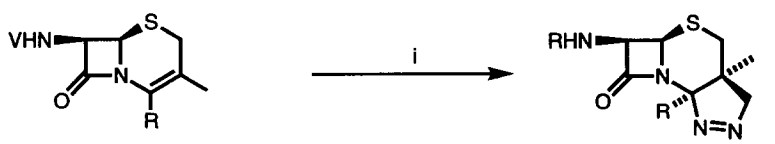
Using the same reaction sequence a 7-β-(D-aminoadipoyl) derivative **76** was also synthesized and used in cyclopropylcarbinyl test experiments. Unfortunately, when **76** was incubated with recombinant deacetoxydeacetylcephalosporin C synthase under standard incubation conditions (Tris·HCl, α-ketoglutarate, ascorbate, Fe(II), dithiothreitol, 2 h, 27 °C) no ring expansion occurred. Compound **76** was found to be only a competitive reversible inhibitor of the enzyme.

The cephem Δ^2 double bond was found to be unreactive towards diazomethane[43] and carbene.[52] However, a



71 R=H
72 R=Ac
73

Figure 12. Synthesis of a 3,4-fused pyrazoline. Reagents: i) AcCl; ii) N_2CH_2, 2 days.



74a R = COOPNB
74b R = COOTCE
74c R = COOMe
74d R = H

75a R = COOPNB
75b R = COOTCE
75c R = COOMe

Figure 13. Synthesis of 3,4-pyrazolinocephalosporins. Reagents: i) N_2CH_2, CH_2Cl_2-ether, rt, 1 week.

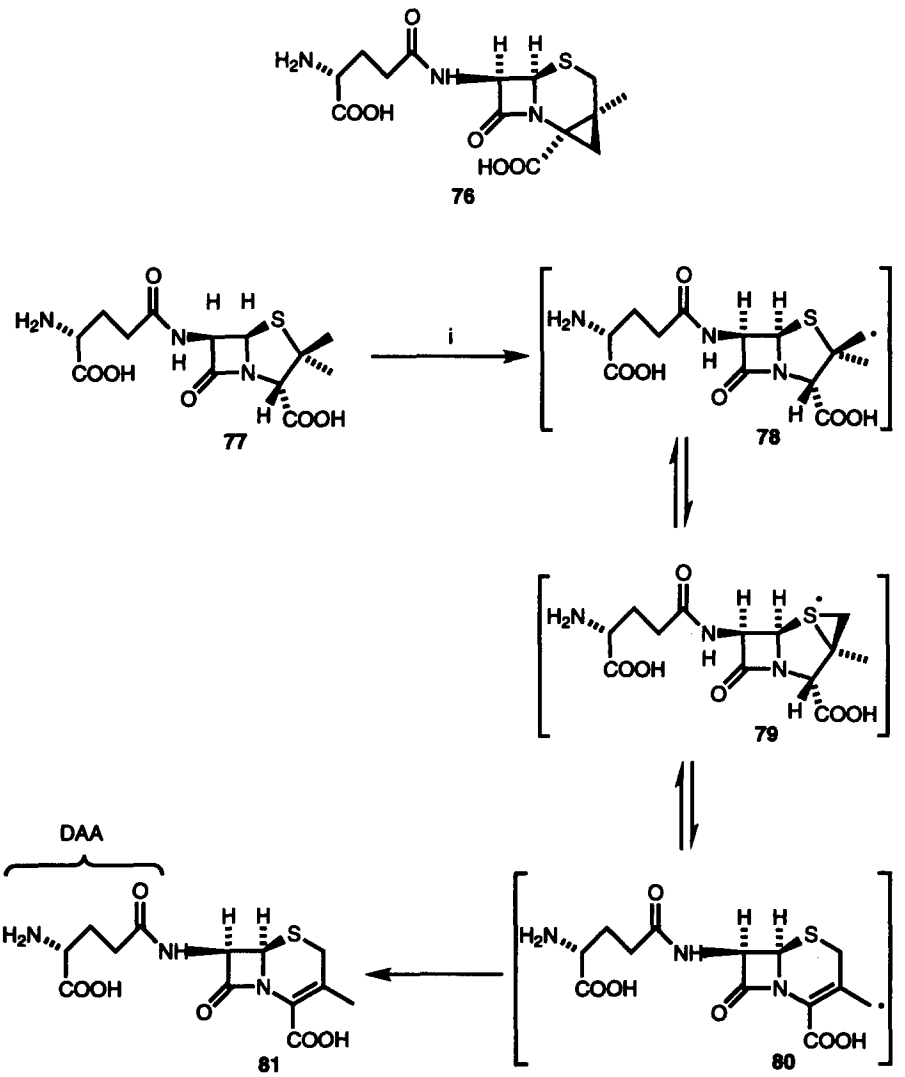


Figure 14. Conversion of penicillin N to deacetoxycephalosporin C. Reagents: i) DAOC/DACS, α-ketoglutarate, Fe(II), O_2.

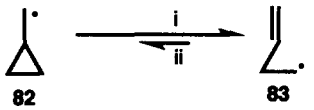


Figure 15. Rearrangement of cyclopropylcarbinyl radicals to allylcarbinyl radicals. Reagents: i) $k_1 = 1.2 \times 10^8\ s^{-1}$, ii) $k_2 = 4.9 \times 10^3\ s^{-1}$.

smooth reaction occurred when it was reacted with a nitrene giving rise to the tricyclic aziridinecephalosporin **95** (Fig. 17).[53]

Recently a Diels–Alder approach was used to obtain novel 2,3-fused cephalosporins.[54] Cephalosporin 1*S*(β)-oxide **96** was converted to a 2-methylenecephem which was subsequently reduced with Zn/Cu couple to give a 2,3-methylenecepham sulphide **97** (Fig. 18). The cephem diene **97** was relatively unreactive towards methyl dithiooxalate requiring 12 h at room temperature to give **98**. Similarly, to obtain the cycloadduct **99** with ethyl methacrylate, 9 h reflux in toluene was necessary. Dienophiles such as maleic anhydride and diethyl azodicarboxylate also reacted but very slowly and formed several by-products.

Structurally related tri- and tetracyclic cephalosporins were obtained in [2 + 2] cycloaddition reactions (Fig 19).[55]

When Heck-type olefination of the triflate **100** was attempted in the presence of palladium acetate and BINAP, a racemic mixture of fused tetracyclic cephems (**102**) formed instead of the desired olefinic products. The use of palladium and BINAP was found to be completely unnecessary. When the reaction was repeated with a range of olefins and acetylenes the corresponding tricyclic cyclobutanes (**103**, **104**) and cyclobutenes (**105**, **106**) formed in good yields. To account for the formation of the products, intermediate formation of an allenic species **101** and a subsequent [2 + 2] cycloaddition reaction was proposed.

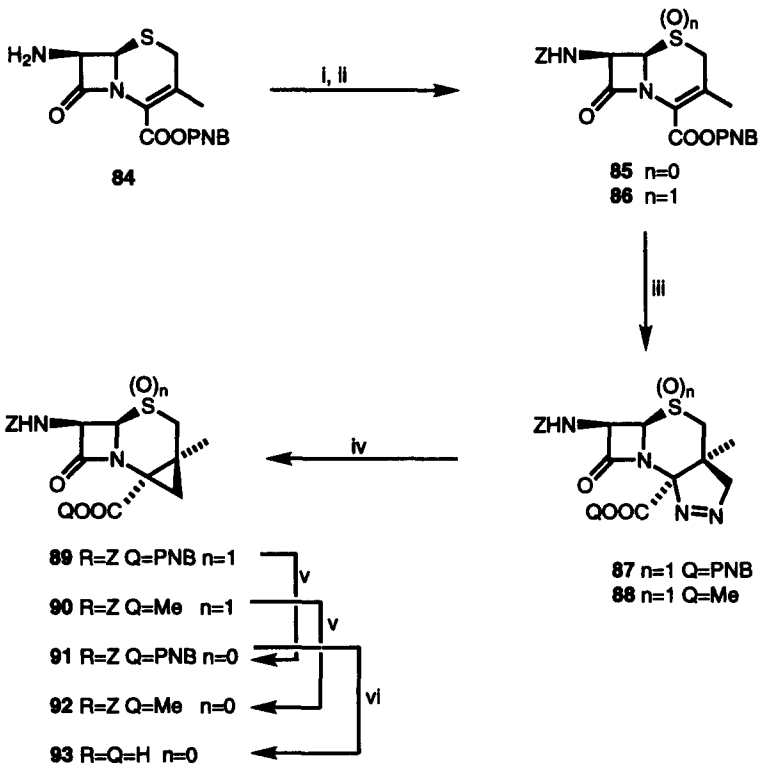


Figure 16. Synthesis of 3,4-cyclopropylcephalosporins. Reagents: i) ZCl, THF, $(C_6H_{11})_2NH$, 0 °C, 8 h; ii) mCPBA, CH_2Cl_2, 0 °C, 30 min; iii) N_2CH_2, CH_2Cl_2, 5 °C, 1 week; iv) xylene, reflux, 3 h; v) AcCl, KI, DMF, 0 °C, 2h; vi) H_2, 10% Pd/C, THF, H_2O, $NaHCO_3$.

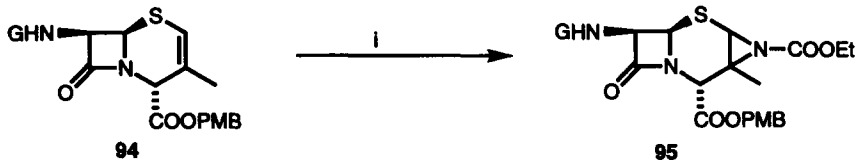


Figure 17. Synthesis of an aziridinecephalosporin. Reagents: i) TsHN-COOEt, CH_2Cl_2, TEA, 21%.

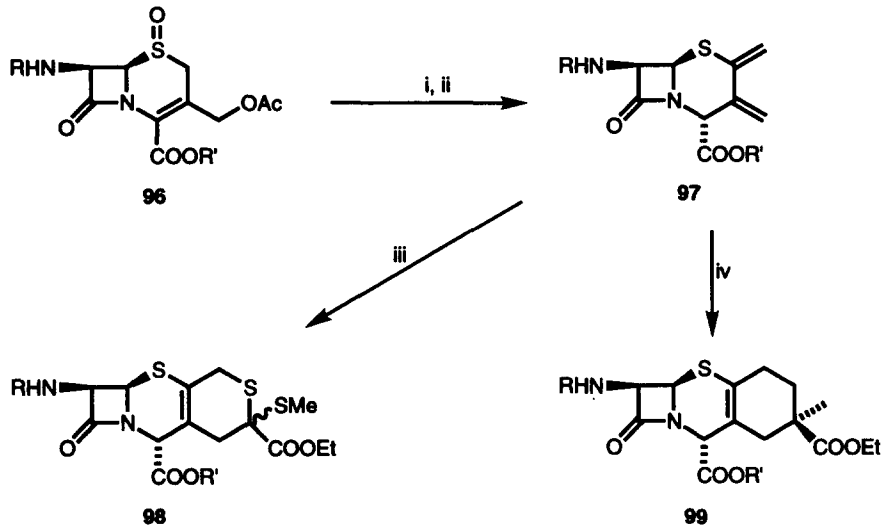


Figure 18. Diels–Alder reactions of 2,3-methylenecephalosporins. Reagents: i) Et_2NH·TFA, HCHO; ii) Zn/Cu, AcOH; iii) MeSC(S)-COOMe, 12 h, rt; iv) H_2C=C(Me)-COOEt, toluene, 90 °C, 9 h.

Though the reaction centre is distant from the stereocentres, surprisingly high stereo- and regioselectivity was observed in the reactions: 1) the substituent on the cyclobutane ring is adjacent to the C-2 position of the cephem nucleus; 2) the cyclobutane ring is on the β-face of the cephem moiety except with Ph and COOMe

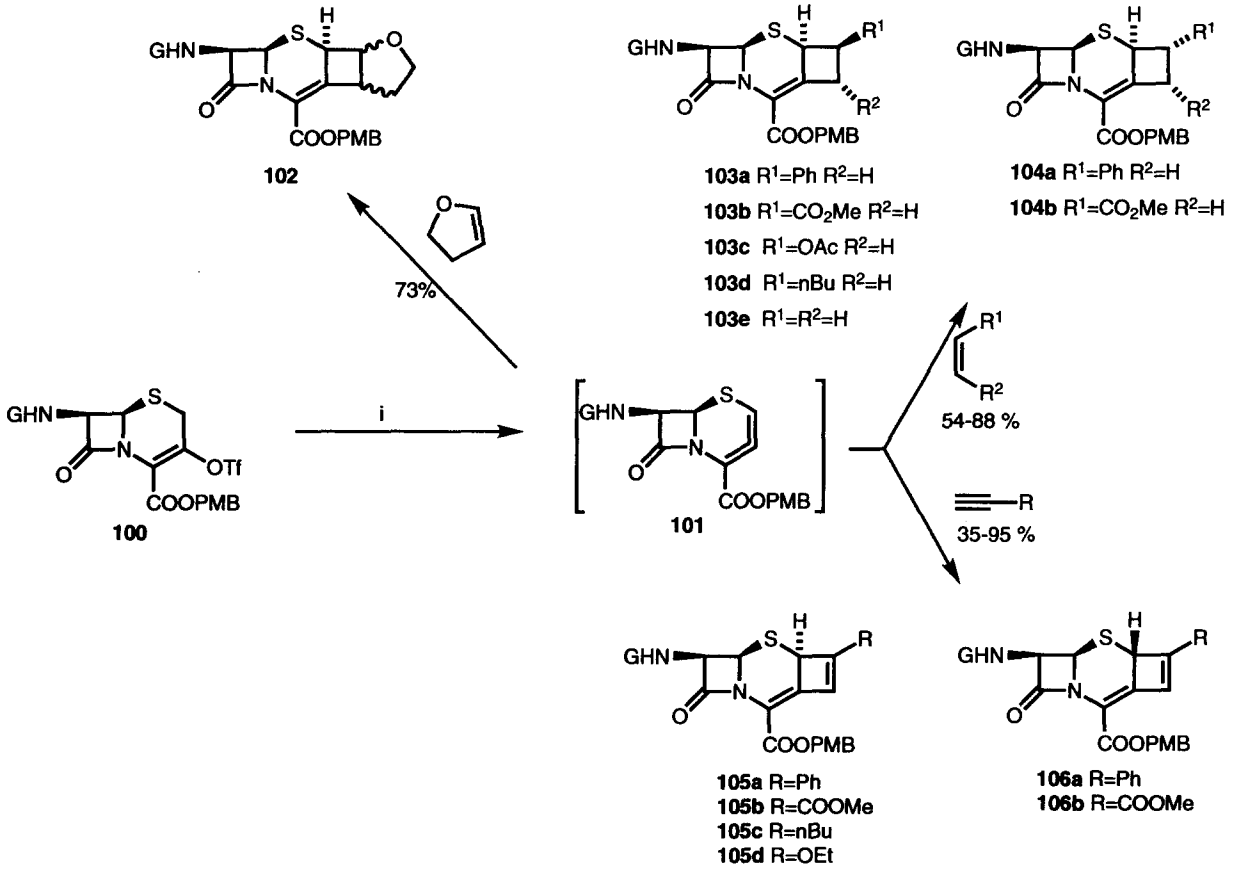


Figure 19. Synthesis of tri- and tetracyclic cephalosporins. Reagents: i) iPr_2NEt, CH_2Cl_2, rt, 15 min.

substituents when racemates form; 3) the proton at C-2 is generally on the α-face of the molecule. However, acetylenes provide C-2 racemic cyclobutenes when phenylacetylene and acetylene carboxylate are used.

Some of the cyclobutane derivatives were found to possess promising antibacterial activity (e.g. **107** in Fig. 20 shows MICs of 0.12 μg mL^{-1} against *E. coli* 10418 and <0.06 μg mL^{-1} against *Haemophilus influenzae* Q).[56]

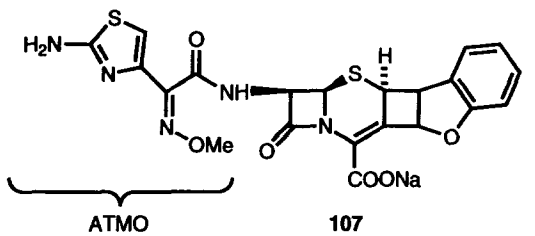


Figure 20. A cyclobutylcephem possessing antibacterial activity.

The scope and limitations of the reaction were further studied using five membered heterocyclic reagents as dienes for [4 + 2] cycloaddition reactions (Fig. 21).[57]

When **100** was reacted with furan, a tetracyclic product formed in 49 % yield. However, instead of being the expected 2,3-fused adduct, it possessed a 3,4-fused structure (**108**). It was envisioned that if the corresponding sulphoxides (**109** and **111**) were used as starting materials, they probably would force the formation of the more stable Δ^3 cephems, i.e. 2,3-fused adducts. Indeed, **110a** and **112** dihydrofurans were obtained in good yields. The configuration of the oxide drastically influenced the stereochemical outcome of the reactions. The *S*(β)-sulphoxide provided a 2-α,9-α-adduct (**110a**), whereas in the case of the *R*(α)-oxide formation of the corresponding 2-β,9-β-product (**112**) was observed. Such differences in reactivity/selectivity between different cephem oxides involving reactions at C-2 (e.g. Mannich-reaction,[16] diazo-exchange reaction,[58] and aldol-condensation[59,60]) were also observed earlier.

When pyrrole derivatives were used as reagents,[57] the N-substituents had significant effect on the structure of the products. Pyrrole and *N*-methylpyrrole failed to react with **100** and **109** by the usual manner. Instead, they provided the corresponding pyrrole substituted cephems **113** and **114**. However, when the reaction was repeated with N-BOC-pyrrole, the desired 2,3-fused compound (**110b**) formed in 29% yield. The author thinks that the diffrerence may lie in the electron distribution of the pyrrole derivatives. The unsubstituted and alkyl substituted compounds are aromatic molecules where Heck reaction takes place, whereas the π-electrons of N-BOC-pyrrole are closer to those of a 1,3-diene and a Diels–Alder reaction is rationalized.

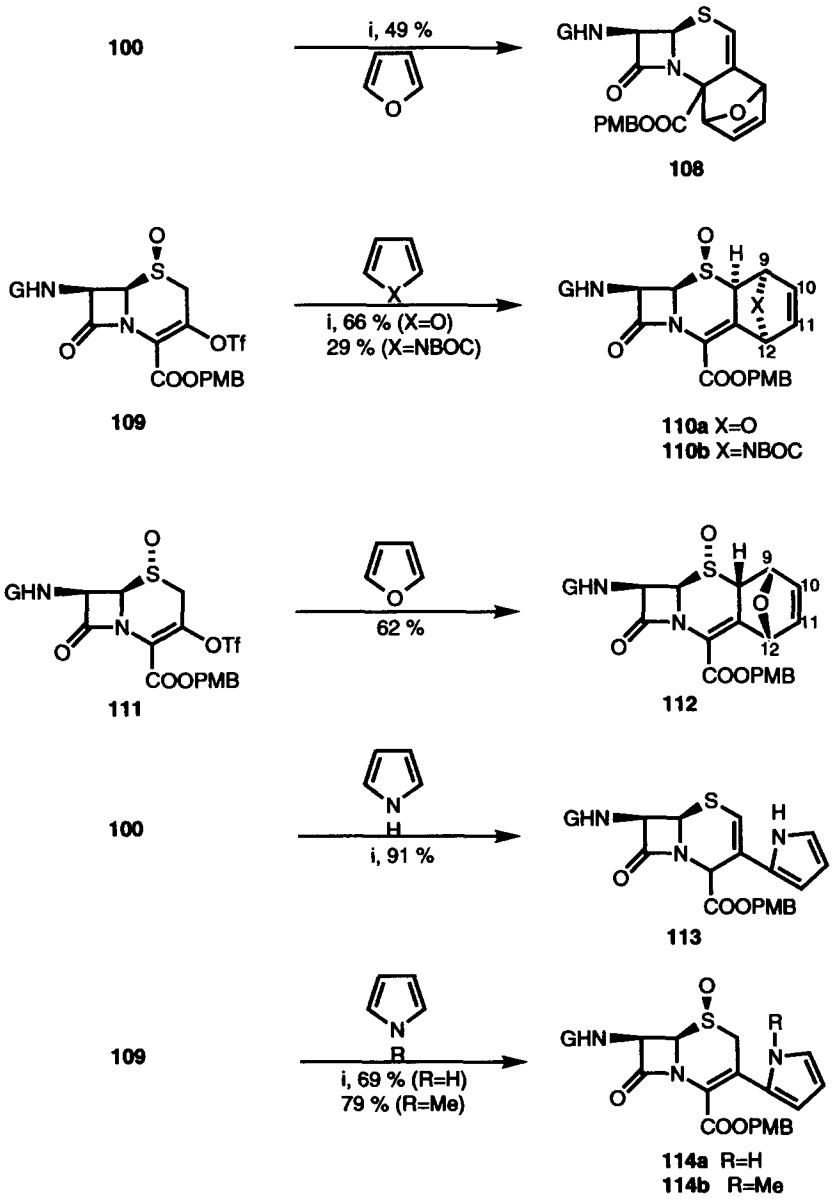


Figure 21. Reactions of cephalosporin triflates with 5-membered heterocycles. Reagents: i) iPr_2NEt, CH_2Cl_2, rt, 15 min.

4. Modifications at C-3

4.1. *3-Spirocyclic derivatives*

For the synthesis of 3-spirocephalosporins, the corresponding 3-*exo*-methylenecephalosporins are ideal precursors and intermediates of several orally active semisynthetic cephalosporins.[61–63] There are several methods for their preparation. They can be divided into two major groups depending on the nature of the key intermediate: 1) syntheses from penicillins by ring-expansion[64–69] via a sulphenium intermediate. These are also the key steps in the synthesis of the oral antibiotics Cefaclor and Cephalexin; 2) Syntheses via C-3 substituted cephalosporins. This method can be subdivided according to the reagents used: a) Raney-Ni cleavage (SR substituent at C-3'),[70,71] b) Zn/H^+ reduction[70,72] [Zn(Hg)[73] and Zn(Cu)[13] are also used] (OAc or SR substituents at C-3'), c) Zn/bis(trimethylsilyl)carbamide/ammonium chloride (SR substituent at C-3'),[72] d) Mg/acetic acid–dichloromethane (SR substituent at C-3')[74] e) $Cr(OAc)_2$/water–DMSO (OAc or SR substituents at C-3').[75,76] f) Electrolysis (OAc or SR substituents at C-3').[77,78]

To the best knowledge of the author little is known of the cycloaddition reactions of 3-methylenecephams.

Compound **115** (Fig. 22) was inactive towards carbene addition.[52,79] Moreover, **115** underwent a 1,3-dipolar cycloaddition reaction with diazomethane only after 7 days at 5 °C in dichloromethane.[79,80] The presence of two β-lactam compounds (**116, 117**) was observed in the reaction mixture (*ca* 7:1 ratio). Following flash chromatography, their 500 MHz ^1H NMR spectra showed that they were not different cycloadducts. The minor product (**117**) arises from a *p*-nitrobenzyl → methyl trans-esterification reaction. The yields were

much higher and the degree of trans-esterification lower when the cycloaddition of a sulphoxide (**118**) was carried out. In this case the **119**:**120** ratio was *ca* 20:1. For analytical purposes a small amount of **119** was synthesized from **116** in a test tube at 0 °C in dichloromethane by oxidation with mCPBA. The pyrazoline sulphoxide obtained in this manner was identical (TLC, ^{1}H NMR) with **119** prepared in the cycloaddition reaction. The finding reveals that oxidation of the sulphur of the dihydrothiazine moiety did not alter the orientation of the diazomethane and did not change significantly the reactivity of the double bond.

The structures of **116–120** and their stereochemistry at C-3 were determined by NMR methods. They were shown to be β-adduct 1-pyrazolines having a 3*S* configuration and were formed in a completely stereo- and regioselective reaction.

A 3-spirocyclopropylcepham (**121**) was obtained along with a second β-lactam when **119** was refluxed in xylene for 3 hours. The physical data revealed that the side product was the 3β-vinylcepham **122**. A mechanism to account for the formation of **122** may be a 1,2-hydrogen shift along with N_2-elimination from the pyrazoline upon heating.

For cyclopropylcarbinyl test experiments in cephalosporin biosynthesis, a D-(α)-aminoadipoyl analog (**127**) (Fig. 23) was also prepared using the same procedure.[49,80]

Compound **127** was then incubated with recombinant DAOC/DAC synthase in the presence of the appropriate co-substrates and co-factors. When the β-lactam 'fingerprint' region of the 500 MHz ^{1}H NMR spectrum (4–5.5 ppm) of the crude incubation mixture was examined, formation of a new β-lactam was detected. By ^{1}H NMR and electrospray MS analysis this was assigned as the 3-hydroxyethylcephem **128**. Formation of **128** may be explained by radical ring opening of the cyclopropane ring. To the best knowledge of the author this is the first example of an α-ketoglutarate-dependent monooxygenase with a homolytic mode of action.

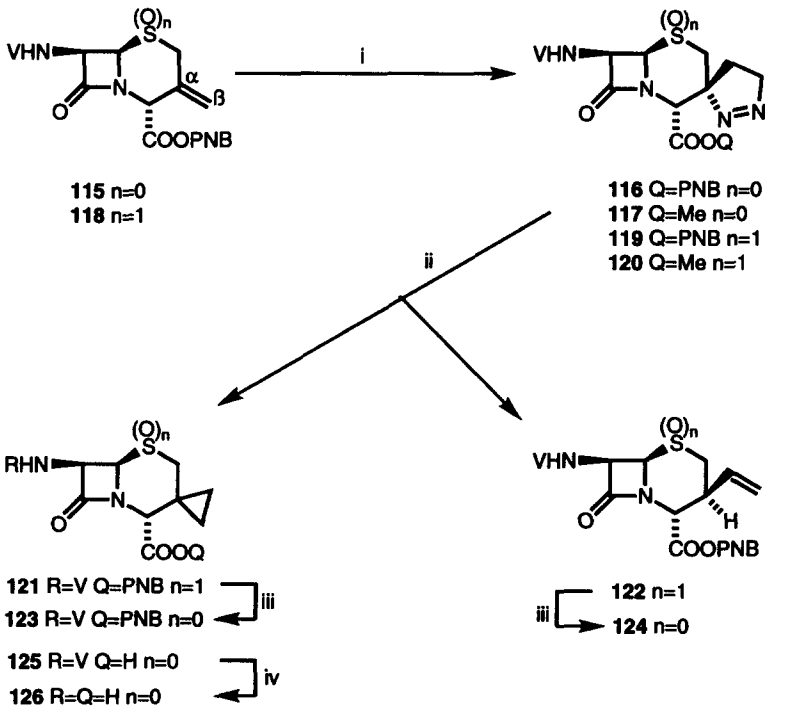


Figure 22. Synthesis of 3-spiropyrazolyl- and 3-spirocyclopropyl cephalosporins. Reagents: i) N_2CH_2, CH_2Cl_2, 5 °C, 1 week; ii) xylene, reflux, 3 h; iii) AcCl, KI, DMF, 0 °C, 2 h; iv) bacterial Penicillin V acylase, HPLC.

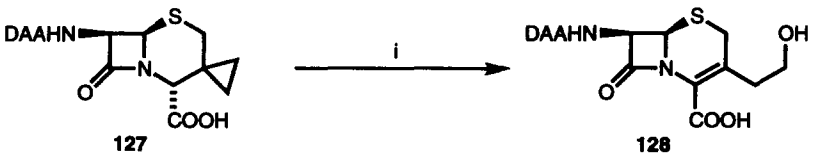


Figure 23. Cyclopropylcarbinyl test experiments in cephalosporin biosynthesis. Reagents: i) recombinant DAOC/DACS, α-ketoglutarate, Fe(II), O_2.

3-Methylenecephams of type **118** did not react with diphenyldiazomethane even on prolonged heating in toluene.[79] However, when the reaction of the 3-methylenecepham sulphide (**115**) and diazo compounds (ethyl diazomalonate, *t*-butyl diazoacetate and diphenyldiazomethane) were carried out in the presence of cuprous sulphate in diethyl carbonate or in dichloromethane, smooth reactions took place. From the reaction mixtures ring expanded exomethylenehomocephams (**130**) were isolated in moderate to good yields (Fig. 24).[81] A plausible mechanism for this rearrangement may involve carbenoid addition to the sulphur atom followed by [2,3]-sigmatropic rearrangement of the resulting intermediate ylide (**129**). When phthalimidonitrene addition to the 3-methylenecephems was attempted, a [2,3]-sigmatropic rearrangement also took place (Fig. 25).[82] Initial formation of a sulfilimine (**131**) by the addition of nitrene to the sulphur atom was followed by spontaneous rearrangement to give 2-aza-4-exomethylenehomocephams (**132**).

Similar [2,3]-sigmatropic rearrangements of 3-methylenecephams were reported earlier.[83,84]

4.2. *Cephem 3'-dipoles*

A C-3 azidocephem (**134**) was prepared from the 3-chloro derivative **133** on treatment with sodium azide in DMF (Fig. 26).[85] Compound **134** was an electron-deficient azide and underwent regioselective cycloaddition reactions with electron rich olefins. However, the triazole adducts were unstable resulting in spontaneous rearrangement via diazonium zwitterionic intermediates to give aziridines, imidates or amidines (Fig. 26).

When the **134** azide was refluxed in methanol–acetone 3-aza- (**139**) and 4-aza-homocephems (**140**) formed probably via nitrene (**141**) and aziridine (**142**) intermediates (Fig. 27).[86]

Willner reported 1,3-dipolar cycloaddition reactions of orally active 3-azidomethylcephems (**143a–c**)[87,88] with acetylenes (Fig. 28.).[89] The 1,2,3-triazoles (**144**) formed in good yield in completely regioselective reactions. Unfortunately, they showed only moderate antibacterial activity. [MICs for **144** (R = Th, R^1 = R^2 = COOMe): 0.16 μg mL^{-1} against *Streptococcus pyogenes* A9604, 0.16 μg mL^{-1} against *S. aureus* Smith A9537, and 8 μg mL^{-1} against *Klebsiella pneumoniae* A9977 versus 0.08, 0.16 and 1.0, respectively for Cephalothin.]

Recently Bi *et al.* reported on the same kind of cycloaddition reactions.[90] The adducts possessing ureido and aminothiazol C-7 side chains showed antibacterial activities superior to Cefotaxime (e.g. 0.72–1.56 μg mL^{-1} against *S. aureus* 209P and 0.2–0.78 μg mL^{-1} against *B. subtilis* versus 1.56 and 0.2 μg mL^{-1}, respectively with Cefotaxime).

A cephem-*N*-methylnitrone **146** (Fig. 29) was also prepared from a 3-formylcephem **145**.[91] Reaction of **146** with methyl acrylate gave rise to the desired isoxazole **147** as a 3:2 mixture of diastereomers. When **146** was reacted with phenylisocyanate a smooth cycloaddition reaction took place to give **148** in good yield. 1,3-Dipolar cycloaddition of **146** with dimethyl acetylenedicarboxylate gave initially the isoxazoline cycloadduct **149**, which underwent spontaneous thermal rearrangement to the oxazoline **150** via an acyl aziridine intermediate.

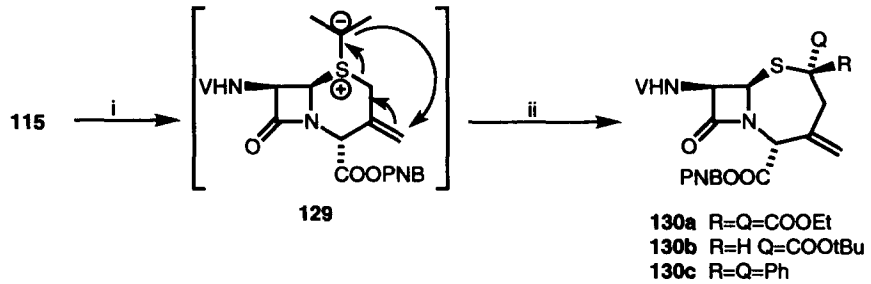


Figure 24. Ring expansion of 3-methylenecephalosporins. Reagents: i) $RQCN_2$, $CuSO_4$, $(EtO)_2CO$ or CH_2Cl_2; ii) spontaneous [2,3]-sigmatropic rearrangement, 45–75%.

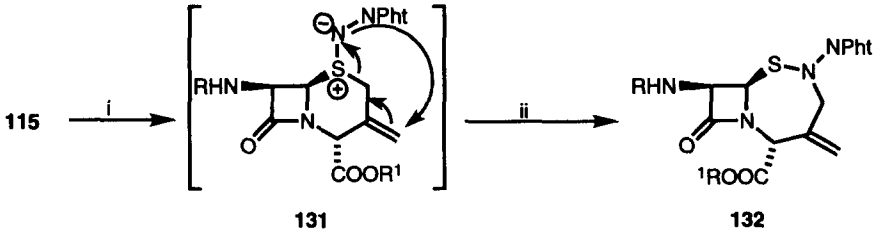


Figure 25. Rearrangement of 3-methylenecephams to 2-azahomocephams. Reagents: i) H_2N-NPht, $Pb(OAc)_4$; ii) spontaneous [2,3]-sigmatropic rearrangement.

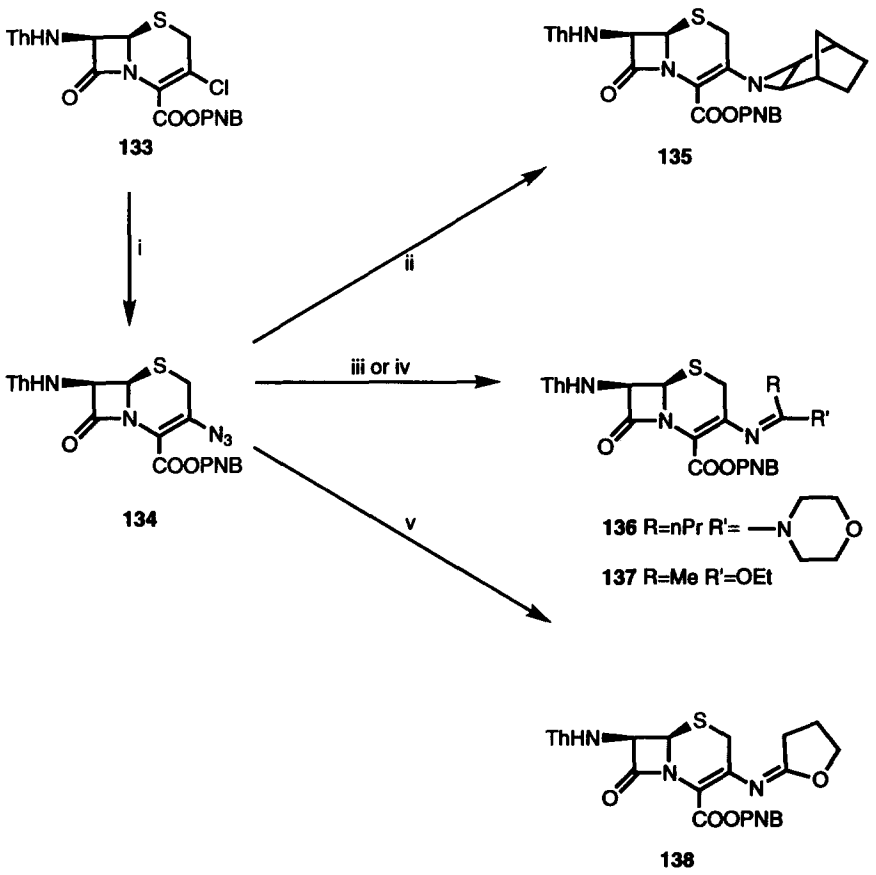


Figure 26. Reactions of a C-3-azidocephem. Reagents: i) NaN_3, DMF, 90%; ii) norbornene, 14%; iii) $EtCH{=}CH\text{-}N(CH_2CH_2)_2O$, rt, 1 h, 62%; iv) $H_2C{=}CH\text{-}OEt$, 33 °C, 45 min, 10%; v) 2-furene, 55 °C, 15 min, 61%.

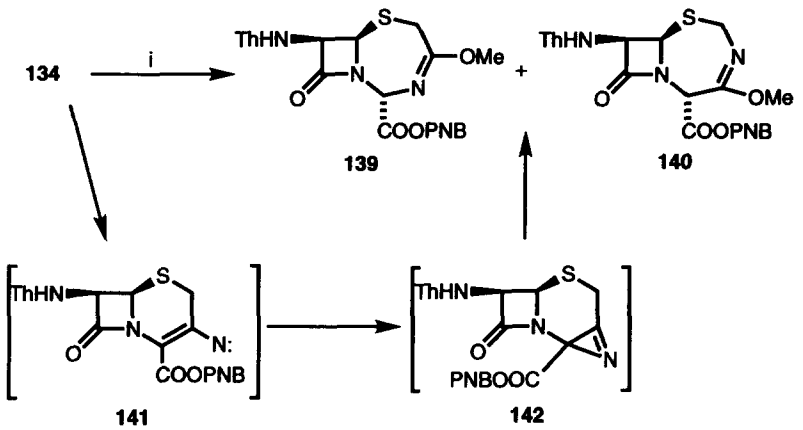
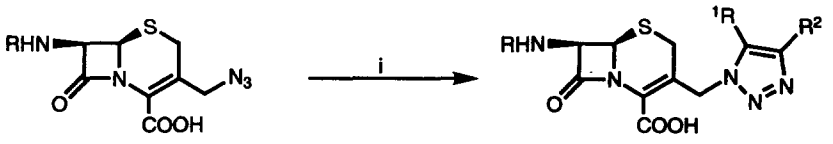


Figure 27. Thermal rearrangement of a C-3-azidocephalosporin. Reagents: i) MeOH, acetone, reflux, 1 h.



143a R=Th
143b R=G
143c R=N(BOC)PG

Figure 28. Reactions of 3-azidomethylcephalosporins with acetylenes. Reagents: i) $R^1\text{-}C{\equiv}C\text{-}R^2$, heat.

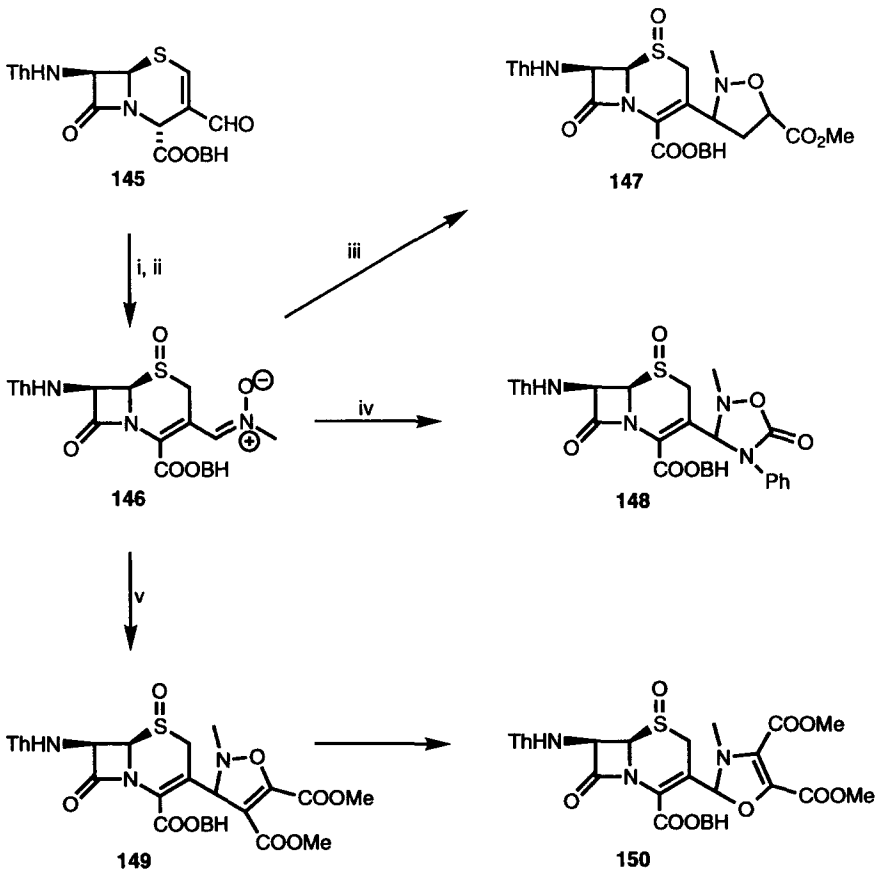


Figure 29. Synthesis and reactions of a cephalosporin *N*-methylnitrone. Reagents: i) MeHN-OH·HCl, pyr., EtOH, heat, 54–60%; ii) mCPBA, CH_2Cl_2, 0 °C, 90%; iii) H_2C=CH-COOMe, 80 °C, 1 h, 52 %; iv) Ph-N=C=O, 52 %; v) MeOOC-C≡C-COOMe, 70 %.

Fahey, Firestone and Christensen synthesized a cephem C-3 nitrile oxide **152** and a 3-diazocephem **154** also from a 3-formylcephalosporin (**151**) (Fig. 30).[92] They were treated with dipolarophiles, e.g. phenyl acetylene, methyl acetylenedicarboxylate, ethyl acrylate and trifluoroacetonitrile providing isoxazoles, 2-pyrazol(in)es and 2-triazoles (**153, 155–7**). The cycloadducts were then converted to the corresponding free carboxylic acids. While their *in vitro* Gram positive activity was quite similar to that of Cephalothin, activity against Gram negative organisms was markedly diminished. Free acids of **153** and **155** had MICs of 3.12 and <0.39 μg mL^{-1} against *S. aureus* MB-2865 and <0.39 μg mL^{-1} against *S. pyogenes* MB-3124.

In an attempt to synthesize homologues of 3-diazocephems and nitrile oxides, an interesting rearrangement, similar to that reported by Lunn[36] (see Fig. 7), took place. When a 3-formylmethylcephem **158** (Fig. 31)[93] was reacted with methylhydrazine, a monocyclic azetidinone **163** formed via ring opening of the cephem dihydrothiazine ring. When **158** was treated with hydroxylamine hydrochloride or hydrazine the primary products **159** and **160** were unstable and cyclized to 3-spiroisoxazoline **161** and spiro-2-pyrazoline **162**, respectively.

4.3. *Cycloaddition reactions of 3-vinylcephalosporins*

3-Vinylcephalosporins, such as Cefixime (FK 027),[94] Cefdinir (FK 482),[95] BMY-28271,[96] CP 6162,[97] Cefprozil (BMY-28100),[98] ME 1207,[99] and BAY V3522[100] are potent and orally active antibacterial agents. Some of them are commercially available drugs or are currently under clinical trial.

The vinylcephalosporins are usually obtained by the following methods: 1) Wittig reactions of 3-formylcephalosporins.[101–4] Potent β-lactamase inhibitors, 7-α-hydroxyethyl(oxa)cephems, were obtained by this method.[103,104] 2) Arbuzov reactions of 3-halomethylcephalosporins and Wittig reactions of the resulting phosphoranes.[94–100] This is the most widely used approach, though it is a long reaction sequence and suffers from low yields. 3) Palladium catalyzed coupling reactions.[105–109] This is the most general approach; however, expensive reagents are needed.

We have improved the second approach[110] and developed a short and relatively high-yielding preparation of the title compounds via 3-iodomethyl derivatives. With a short route to 3-vinylcephalosporins in hand, we have decided to use them as synthons for the synthesis

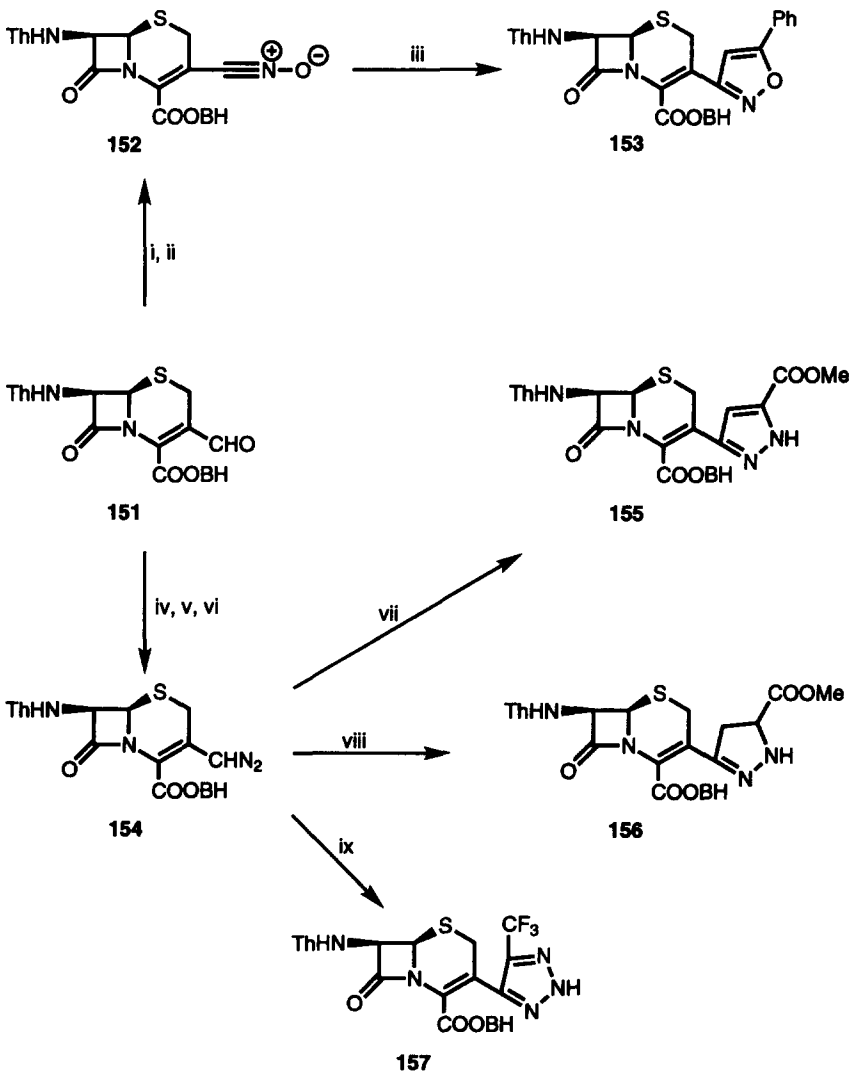


Figure 30. Synthesis and reactions of cephem C-3 nitrile oxides and 3-diazomethylcephalosporins. Reagents: i) H_2N-OH·HCl, iPrOH, 10 min; ii) 2 eq. $Pb(OAc)_4$, -78 °C, CH_2Cl_2; iii) Ph-C≡CH, rt, 30 min; iv) H_2N-NHTs, $CHCl_3$, 15 min, 25 °C; v) nBuLi, THF; vi) -78 °C → 40 °C; vii) HC≡C-COOMe, 50–55 °C, 24 h; viii) H_2C=CH-COOEt; ix) F_3C-C≡N, 5 days.

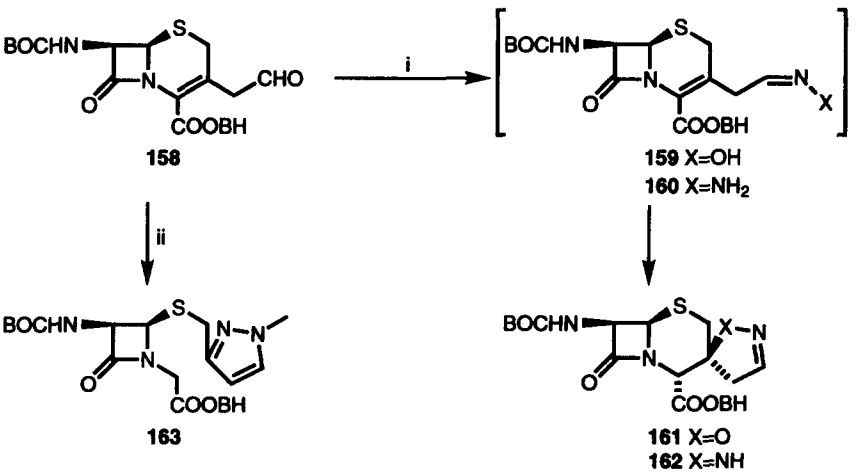


Figure 31. Formation of 3-spirocyclic cephalosporins. Reagents: i) MeHN-OH·HCl, pyr., EtOH or H_2N-NH_2, EtOH; ii) MeHN-NH_2, EtOH.

of novel C-3-heterocyclic cephems. Firstly, the 1,3-dipolar cycloaddition reactions with diazoalkanes were examined.[111-114]

When **164** (Fig. 32) was allowed to react with a large excess of diazomethane at room temperature in dichloromethane ether a single product was detected after 5 min (TLC) but before the completion of the reaction (1 h) the formation of two additional products (**167** and its epimer) in different quantities was observed. When the 3-vinylcephalosporin 1*S*(β)-oxide **165** was reacted with diazomethane, the cycloaddition reaction was complete only after 4 h and a single product **168** was observed in a stereo- and regioselective reaction. The products of the cycloaddition reaction were unambiguously assigned by extensive NMR studies as the 3-pyrazolylcephems **166** and **168**, and the double adduct 3,4-pyrazolino-3-pyrazolylcepham **167**.

Surprisingly, the 1,3-dipolar cycloaddition reaction of the vinylcephalosporin **164** with diphenyldiazomethane occurred only after 40 h reflux in dichloromethane to give the epimeric mixture of **169** in the ratio of 2:1. The Δ^3 double bond of the molecule was unaffected by this reaction. The configurational and conformational analyses of the cycloadducts were carried out by NMR and molecular modelling.[112,114]

Spry has used a palladium–acetate catalyzed cyclopropanation approach to synthesize 3-cyclopropyl-(carba)cephalosporins **172** and **173** from 3-vinyl(carba)-cephalosporins **170** and **171** (Fig. 33).[115]

Substituted vinylcephems as well as Δ^2 and Δ^3 cephems did not react under the same conditions. Other Pd compounds were less effective, and Rh catalysts were totally ineffective. The cyclopropanes were converted into the corresponding phenylglycine (**174, 175**)

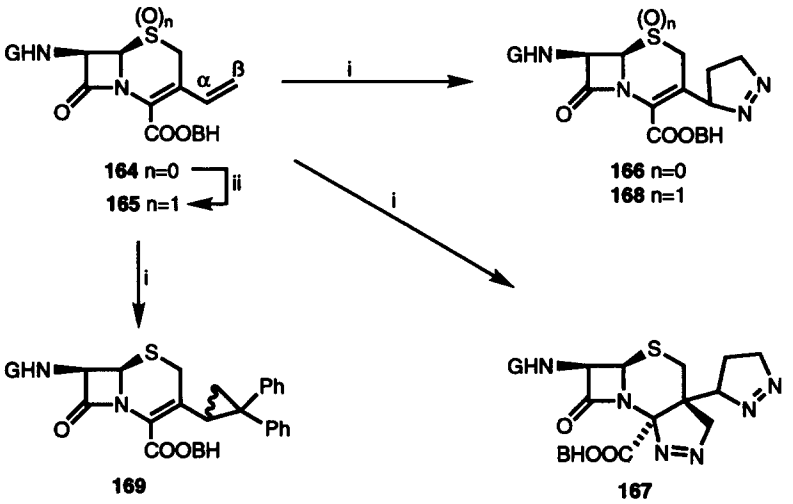


Figure 32. Reactions of 3-vinylcephalosporins with diazoalkanes. Reagents: i) N_2CH_2, CH_2Cl_2, rt, 1–4 h or i) N_2CPh_2, CH_2Cl_2, reflux, 40 h; ii) mCPBA, CH_2Cl_2, 0 °C, 30 min.

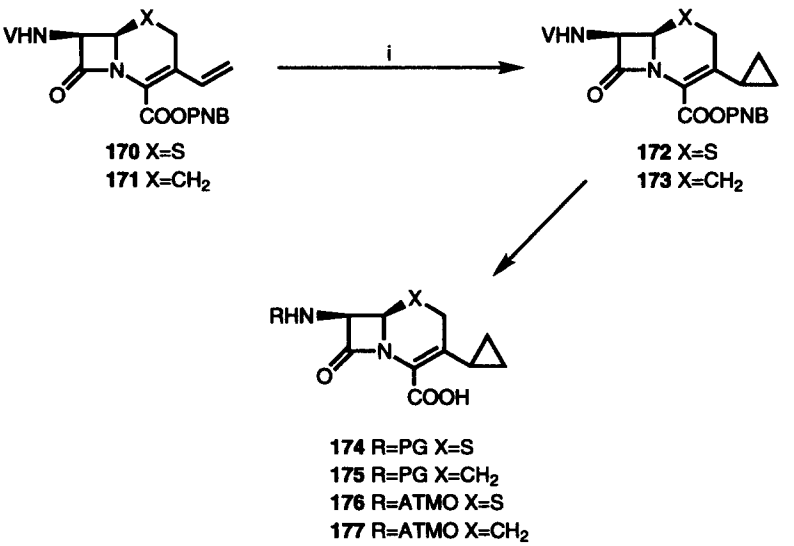


Figure 33. Synthesis of 3-cyclopropylcephalosporins. Reagents: i) 10–20 eq. N_2CH_2, 0.5 eq. $Pd(OAc)_2$, CH_2Cl_2, 5 °C, 60% (X = S), 90% (X = CH_2).

and 2-(aminothiazol-4-yl)-2-(Z)-alkoxyimino-acetamido derivatives (**176, 177**). These were more active than Cephalexin or Cefaclor but less active than the corresponding 3-vinylcephems (Table 3).

In an independent paper the synthesis of similar 3-cyclopropylcephems were reported using practically the same approach.[116]

Fell has used substituted vinylcephalosporins in 1,3-dipolar cycloadditions with diazomethane and studied the regioselectivity of the reaction (Fig. 34).[117] It was found that when 3-vinylcephems with electron donating substituents [H, Ph, methylthiazol (MT)] (**178a–c**) were reacted with excess diazomethane, β-adduct 1-pyrazoles (**179**) were formed regio- and stereoselectively. However, when carbomethoxy substituted vinylcephalosporins were used (**178d,e**), α-adducts (**181, 182**) were isolated. Reaction of the vinyl ester **178d** gave, after isomerization of the initially formed 1-pyrazoline, the 2-pyrazoline **181** bearing the more stable α,β-unsaturated ester. When the ketomalonate derivative **178e** was reacted with diazomethane, loss of stereoselectivity was observed and the isomeric mixture **182** was isolated. Compounds **179** and **182** were transformed to the corresponding cyclopropanes (**180, 183**). Unfortunately, none of the derivatives exhibited significant antibacterial activity (no data given).

Table 3. Antibacterial activities of 3'-cyclopropylcephalosporins

	MIC values (μg mL^{-1})						
	Cephalexin	**174**	**175**	**176**	**177**	Cefaclor	Cefixime
Staphylococcus aureus XII	4	0.25	0.5	8	0.25	1	16
Streptococcus pyogenes C203	1	0.06	0.125	0.008	0.25	0.125	0.125
Streptococcus pneumoniae PK	1	0.5	2	0.06	4	1	0.125
Enterococcus faecalis 2041	128	32	128	4	4	32	8
Haemophilus influenzae (β-lactamase producer)	8	4	8	0.06	0.5	1	0.03
Enterobacter cloacae EB5	64	64	128	2	4	4	1
Serratia marcescens SE3	128	32	128	4	16	32	0.5
Morganella morganii PR15	128	128	128	1	0.5	128	0.25

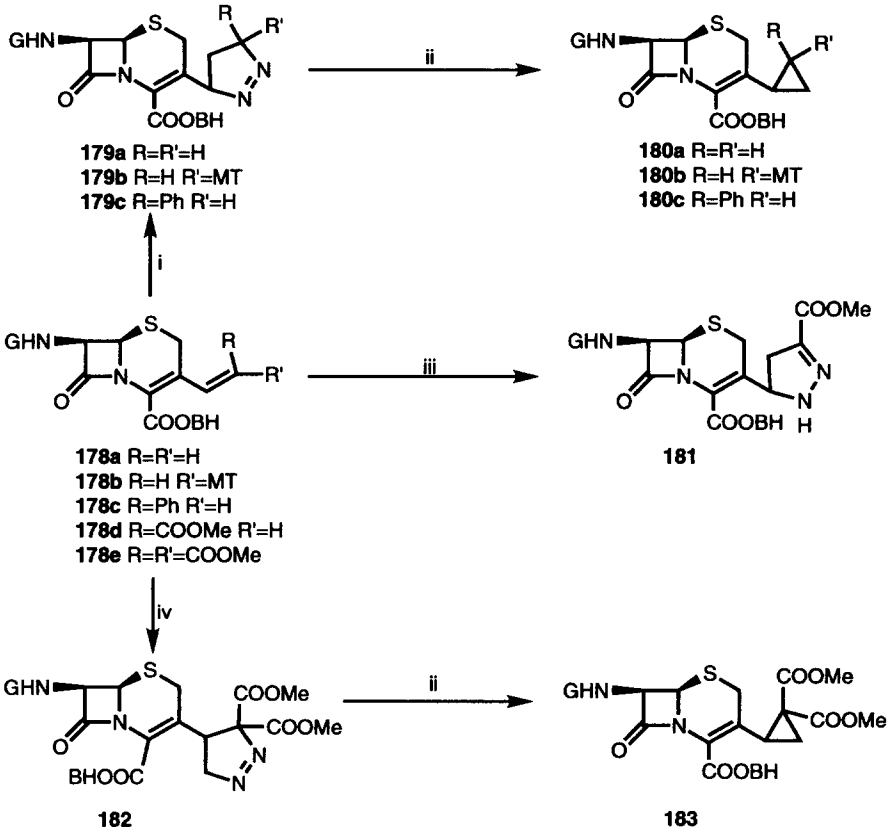
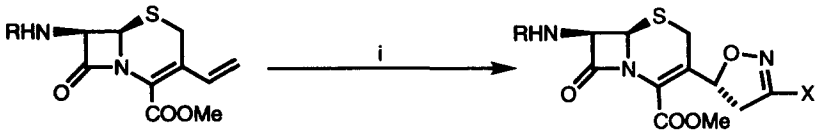


Figure 34. Regioselectivity in the 1,3-dipolar cycloadditions of substituted 3-vinylcephalosporins with diazomethane. Reagents: i) N_2CH_2, CH_2Cl_2-ether, rt, 3–4 h ; ii) heat; iii) step 'i' with **162d**; iv) step 'i' with **162e**.

We have extended the 1,3-dipoles used in cycloaddition reactions with vinylcephalosporins to silyl nitronates (Fig. 35).[118] Compound **184a** and **b** were reacted with silyl nitronates of nitromethane, nitroethane and 1-nitropropane. Ethyl nitroacetate and similarly functionalized primary nitroalkanes could not be used due to undesired side reactions. The vinyl function of **184** was rather unreactive towards the 1,3-dipole; the reaction took three days on standing at room temperature giving compound **185** in a completely stereo- and regioselective manner. Unfortunately, under the basic reaction conditions, partial (*ca* 30%) $\Delta^3 \rightarrow \Delta^2$ isomerization of the cephem double bond also occurred. Formation of the Δ^2 isomer was avoided when a mild base, *N,N*-tetramethylurea, was used rather than triethylamine. The Δ^2 isomer did not react with silyl nitronates.

Compound **184** failed to react with nitrile oxides generated from nitroalkanes with phenylisocyanate in the presence of triethylamine or *N,N*-tetramethylurea.[118] However, smooth reaction was observed when the vinylcephem **186** was treated with nitrile oxides prepared from chloroaldoximes (Fig. 36).[119] The 3-(isoxazolin-5-yl)cephalosporins (**187**) formed as mixtures of diastereomers (*ca* 1:1 ratio) in excellent yields. In the case of a dimethylamino derivative **188** opposite regioselectivity and spontaneous amine elimination was observed giving the 3-(isoxazol-4-yl)cephalosporin **190**. The free carboxylic acids displayed moderate antibacterial activities against both Gram positive and Gram negative bacteria (Table 4).

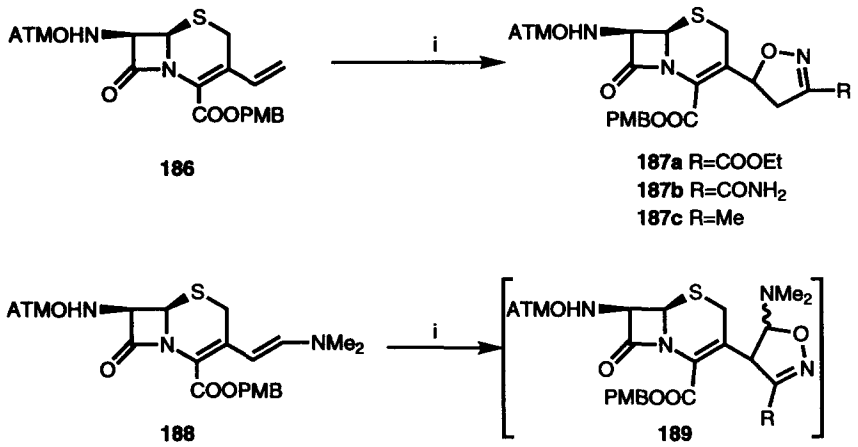
Highly active antibacterials were obtained when nitrone cycloadditions of vinylcephems were carried out (Fig. 37)[120] The reaction proceeded regioselectively and with moderate stereoselectivity (*S*:*R* = 3:1). The 3-(isoxazolin-5-yl)cephems (**192**) were converted into the corres-



184a R=G
184b R=V

185a R=G X=H
185b R=V X=H
185c R=G X=Me
185d R=G X=Et

Figure 35. Asymmetric synthesis of 3-(isoxazol-5-yl)cephems using silyl nitronates. Reagents: i) TMSCl, XCH_2NO_2, TEA, absolute CH_2Cl_2, rt, 3 days, N_2 atmosphere.

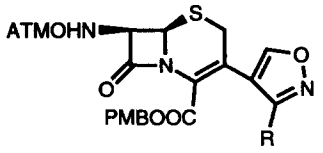


186

187a R=COOEt
187b R=$CONH_2$
187c R=Me

188

189



190a R=COOEt
190b R=$CONH_2$

Figure 36. 1,3-Dipolar cycloaddition reactions of 3-vinylcephems with nitrile oxides. Reagents: i) R(Cl)C=N-OH, base.

Table 4. Antibacterial activities of 3'-(isoxazol(id)in-5-yl)-3-(isoxazolidinium-5-yl)- and 3-(isoxazol-4-yl)cephalosporins

	MIC values (μg mL^{-1})						
	187a(3'*S*)	**187b**(3'*S*)	**190a**	**190b**	SPD391	**193**	CAZ
Staphylococcus aureus FDA 209P	6.25	6.25	6.25	6.25	25	12.5	12.5
Bacillus subtilis ATCC 6633	0.39	0.39	0.78	1.56	3.13	3.13	3.13
Escherichia coli K12 W3630 Rms212 (penicillinase producer)	0.78	0.39	3.13	3.13	0.006	0.05	0.39
Klebsiella pneumoniae PCI 602	0.1	0.025	0.025	0.1	0.003	0.025	0.20
Enterobacter cloacae GN 7471 (cephalosporinase producer)	100	50	>100	>100	6.25	6.25	3.13
Proteus vulgaris OX-19	0.39	0.78	0.1	0.2	0.39	6.25	0.05
Proteus vulgaris GN7919 (cefuroximase producer)	50	100	25	6.25	12.5	12.5	3.13
Pseudomonas aeruginosa IFO3345	>100	>100	>100	>100	0.1	0.2	0.78

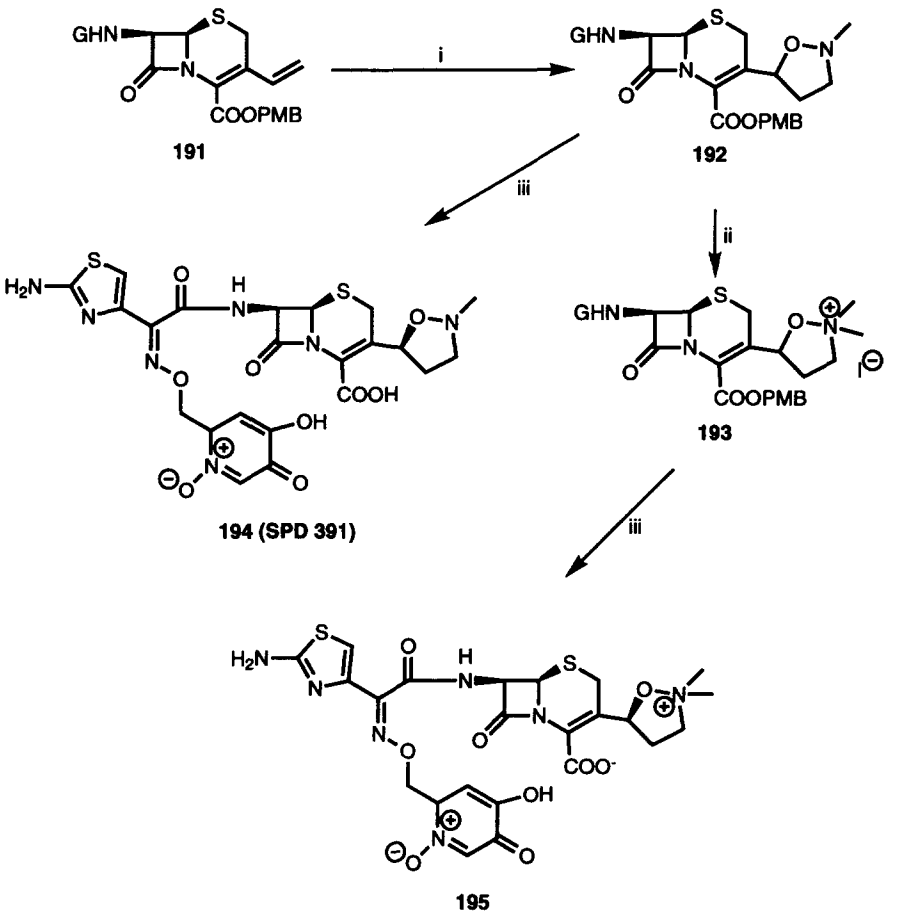


Figure 37. 1,3-Dipolar cycloaddition reactions of 3-vinylcephems with *N*-methylnitrone. Reagents: i) MeNH-OH·HCl, CH_2O, NaOAc, 90 °C, 82%; ii) MeI; iii) deprotection and trans-acylation.

ponding isoxazolidinium salts (**193**) upon treatment with methyl iodide. The configuration at the C-3' position greatly influenced the antibacterial activities (the 3'*S* diastereomer was generally four times as active as the corresponding 3'*R* epimer). Quaternization of the isoxazolidine ring markedly enhanced the activity against both Gram positive and Gram negative bacteria. Two of the novel cephalosporins (**194**, **195**) displayed higher antipseudomonal activity than Ceftazidime (Table 4).[121,122]

Orally active pivaloyloxymethyl 3-(isoxazolidin-5-yl)-cephalosporins were also synthesized by this approach (ED_{50} = 2.5–23 mg kg^{-1} versus 8 – >50 mg kg^{-1} for Cefetamet pivoxyl).[123]

Surprising results were reported on phthalimidonitrene addition experiments of 3-vinyl(carba)cephalosporins (**170**, **171**) (Fig. 38).[82] In the case of the **171** carba analogue the nitrene added to the generally rather unreactive endocyclic Δ^3 double bond providing a 3,4-aziridinecepham (**197**). The thia analogue (**170**) gave the aziridine (**198**) which rearranged to a 3-vinyl-Δ^2-cephem (**199**).

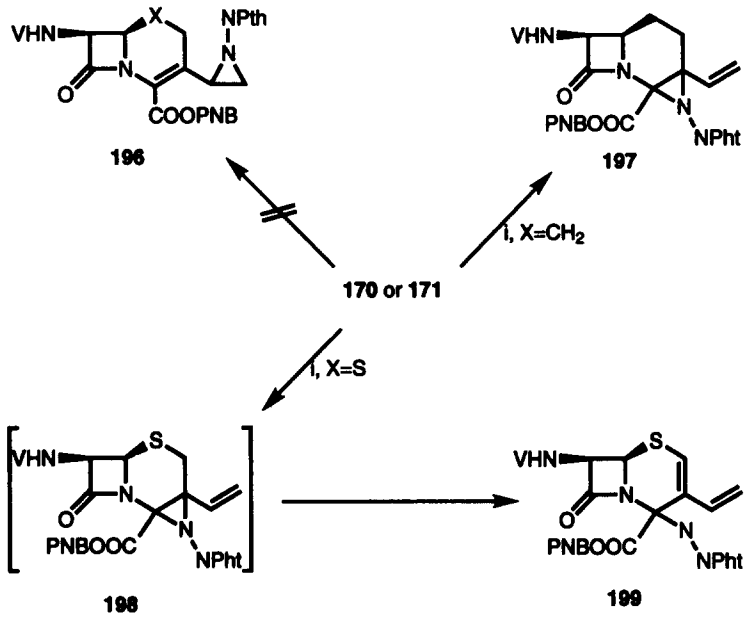


Figure 38. Reaction of 3-vinylcephems with phthalylnitrene. Reagents: i) H_2N-NPht, $Pb(OAc)_4$.

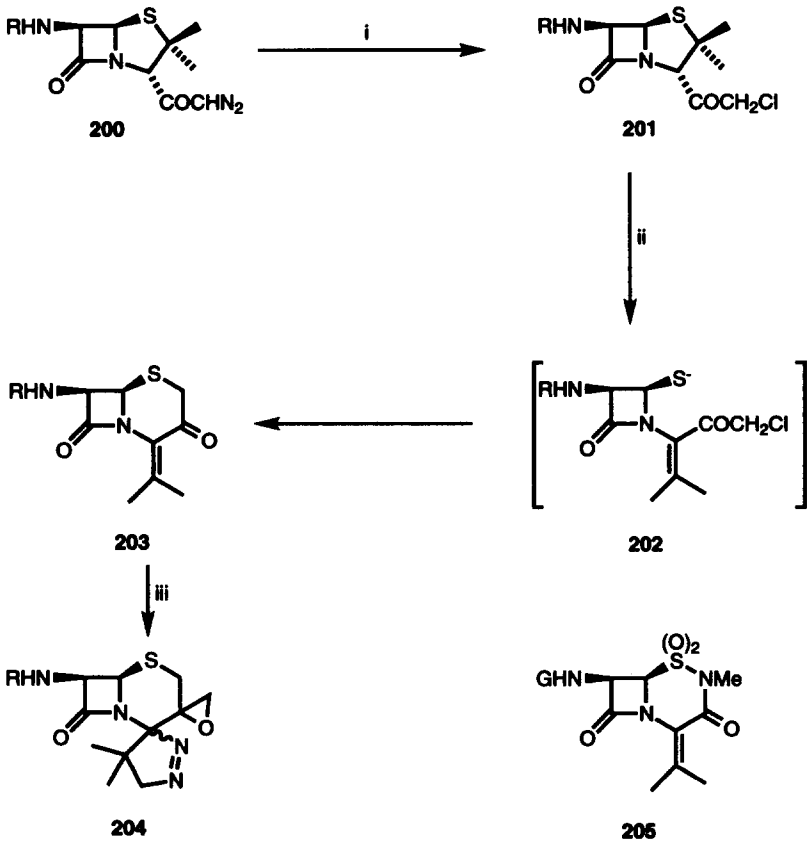


Figure 39. Synthesis of 4-pyrazolinocephams. Reagents: i) 1 eq. 1N HCl in Me_2CO; ii) 1 eq. TEA in CH_2Cl_2; iii) excess CH_2N_2.

5. Modifications at C-4

To the best knowledge of the author only one example has been published on the 1,3-dipolar cycloaddition modification of cephalosporins at C-4 (Fig. 39).[124]

A penicillanoyldiazomethane (**200**) was treated with dilute hydrochloric acid to provide the key precursor chloroketone **201** in 60% yield.[125,126] Compound **201** underwent base promoted β-elimination to afford the enethiolate **202** which ring closed to a 3-keto-4-isopropylidenecepham (**203**). When **203** was subjected to 1,3-dipolar cycloaddition reaction with a large excess of diazomethane diastereomeric mixtures of 3-

spiroepoxy-4-spiropyrazolinocephams (**204**) formed.[124] These compounds were unstable to transfer into other cephalosporin derivatives.

Recently, aza analogues of **203** (e.g. **205**) were reported to possess antitumour activity.[127,128]

6. Modifications at C-7

6.1. *Cephalosporin C-7 dipoles*

Relatively little has been reported on this kind of modification at C-7. A smooth cycloaddition of the 1,3-dipole generated from the iminochloride **206** was reported with diethyl azodicarboxylate to give a spirotriazole (**207**) (Fig. 40).[129] Unfortunately, under the basic conditions partial $\Delta^3 \rightarrow \Delta^2$ isomerization also took place. The reaction processed better in the penicillin series.

Diazopenicillanates were used for the synthesis of spirocyclic pyrazolines and cyclopropanes[130] but the investigation was not extended to the cephalosporin series.

Using a totally different approach diazocephalosporanates were converted to spiroepoxycephalosporins (**209**),[131] analogues of the β-lactamase inhibitor spiroepoxypenicillins (**208**) (Fig. 41).[132]

6.2. *Cycloaddition reactions of C-7-alkenylcephalosporins*

C-7-Alkenylcephalosporins are structural analogues of the β-lactamase inhibitor 6-alkenylpenams,[133–137] 6-alkenylpenems,[138–143] 6-alkenyloxapenems,[144] 3-alkenylazetidinones,[145–147] and 6-alkenylcarbapenems (asparenomycins).[148–150] Surprisingly, only a few cephalosporin derivatives of this kind were prepared and their cycloaddition reactions were not studied. The only examples are known in the penicillin[130] and monocyclic β-lactam series.[151]

Acknowledgements

The author thanks Dr Greg (Kiwi) Lynch and Professor Craig A. Townsend for proof reading the manuscript, Professor Ferenc Sztaricskai for advice and encouragement. This publication was supported partially by Grant No. 1 F05 TWO5111-01 from the Fogarty International Center (FIC), National Institutes of Health (NIH). Its contents are solely the responsibility of the author and do not necessarily represent the official views of the FIC, NIH.

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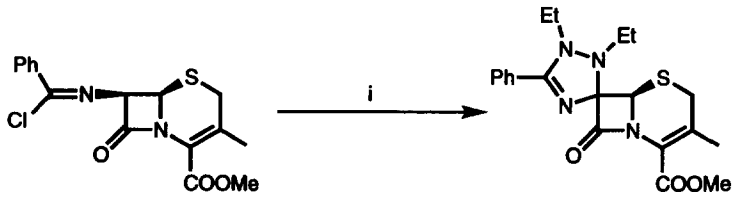

206 **207**

Figure 40. Synthesis of 7-spirotriazolocephems. Reagents: i) EtOOC-N=N-COOEt, DBN, THF, 38%.

208 **209**

Figure 41. Spiroepoxy β-lactams, novel β-lactamase inhibitors.

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(*Received in U.S.A.* 10 *November* 1994; *accepted* 28 *March* 1995)

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