SUMMARY

Cephalosporins (4) occupy a very important place among the broad spectrum antibiotics. In particular they have found increasing use in combatting infectious diseases in man and animal, because of their high anti-biotic potency and the virtually complete absence of toxic effects towards mammalian organism.

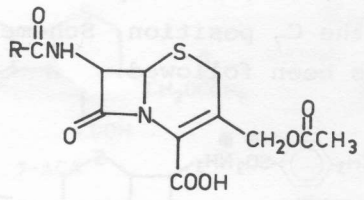
Although the naturally occuring cephalosporin C (4,R = aminoadipyl) is not being used clinically, exceedingly useful drugs have been obtained by replacing the group R in 4 by a variety of organic side chains. These compounds are called semi-synthetic cephalosporins. Although at first glance the replacement of R by a different organic moiety appears to entail a few simple organic reactions, the multifunctionality of cephalosporins (amide, β-lactam, carboxylic acid, olefin, sulfide, allylic protons etc.) force the synthetic organic chemist to devise sophisticated methods in order to succesfully transform the natural product to the desired drug in an industrially viable manner.

Of the hundreds of semi-synthetic cephalosporins which have been prepared no example is known to us in which the entire amino group at C_7 has been replaced by a carbon chain.

The aim of the work described in this dissertation was the synthesis of cephalosporins 11 in which the entire C_7 amine function was replaced by an alkyl or functionalized alkyl group.

In order to introduce such an alkyl side chain, which is in fact the replacement of an amine by a methylene

group, we made use of a reaction between trialkylboranes and diazoamides.



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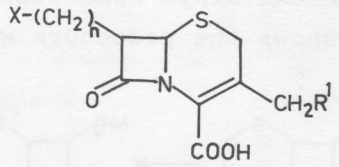


11 R= H, $OCOCH_3$

X= H, amide, ester

At the time our research started the reaction between trialkylboranes and ethyl diazoacetate to form esters under very mild conditions (fig. 5.2), had been briefly reported by Hooz. After considerable modification of the reported

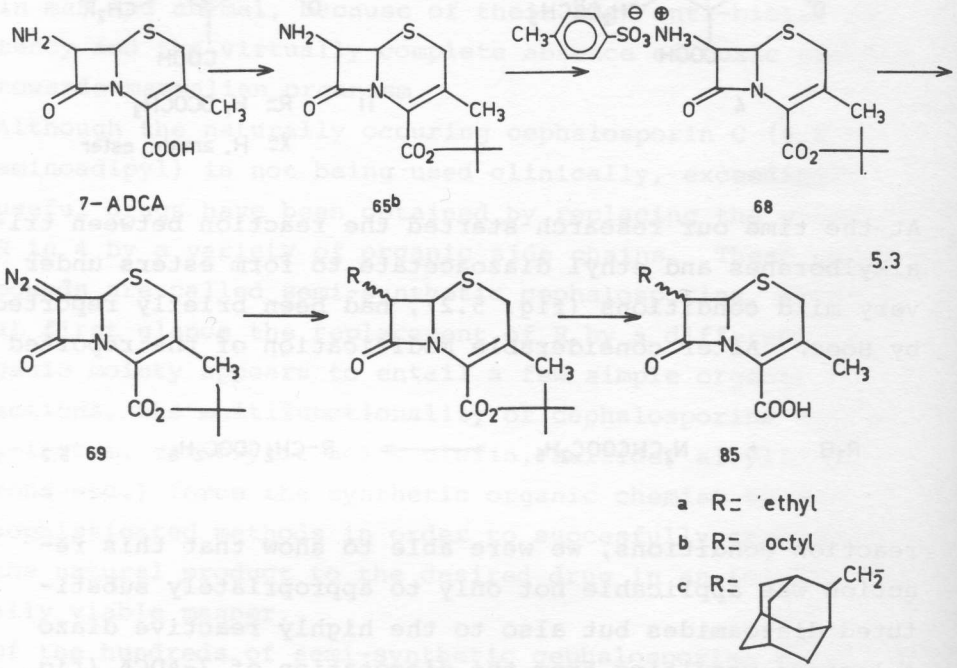
$$R_3B + N_2CHCOOC_2H_5 \longrightarrow R\text{-}CH_2COOC_2H_5 \qquad 5.2$$

reaction conditions, we were able to show that this reaction was applicable not only to appropriately substituted diazoamides but also to the highly reactive diazo β-lactams resulting from the diazotation of 7-ADCA (fig. 5.3) and 7-ACA (fig. 5.4).

In chapter 2 the reaction of different trialkylboranes with ethyl diazoacetate is described. The synthesis and alkylation of 1-(α-diazoacetyl)-pipiridine with trioctylborane is dealt with, as an example of this type of alkylationreaction with diazoamides.

In chapter 3 the problem of selectively protecting the carboxylic acid group during the synthesis of 11, is discussed and an efficient synthesis is given for tert-butyl 7-diazodeacetoxycephalosporanate (69). Optimum conditions

for the reaction of trialkylboranes and monochloroalkylborane with 69 are outlined. The result is the synthesis of the new cephalosporins 85^a, 85^b, 85^c, which possess different alkyl substituents at the C_7 position. Scheme 5.3 shows the procedure which has been followed.



5.3

The stereochemistry of this reaction is discussed and the biologically critical configuration of the 7 position is given.

In chapter 4 an efficient synthesis of tert-butyl 7-diazocephalosporanate (99) and the reaction of the latter with functionalized organoboranes is described. The problems of selective hydroboration of functionalized alkenes is dealt with and the synthesis of 7-(4-benzoyloxybutyl)-cephalosporani acid (104)according to scheme

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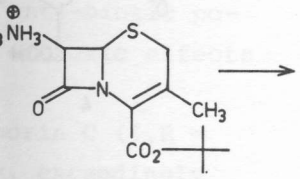

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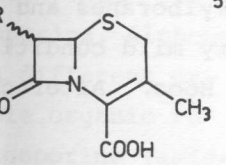
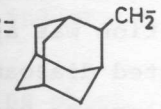
5.3



85

a R= ethyl
b R= octyl
c R= 

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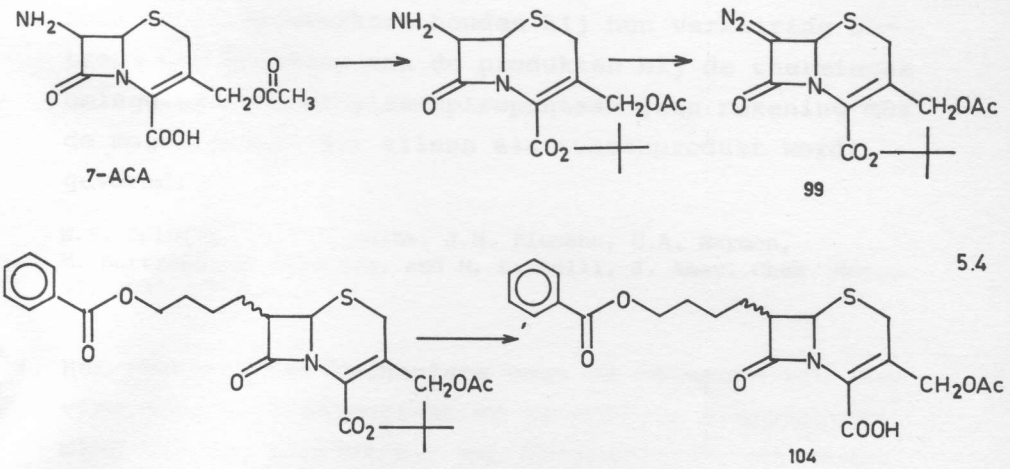

7-ACA

99

104

5.4

Finally, in chapter 5, the *in vitro* screening results of the novel alkylated cephalosporins are given. Preliminary results indicate low but definite anti-biotic activity of the semi-synthetic cephalosporin 85[c].

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