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Approaches to the Synthesis of 2-Sila-1-carba-cephalosporins

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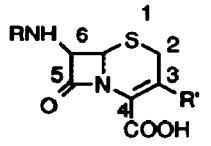
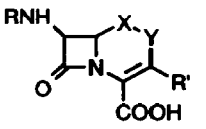
Abstract: *A condensed β-lactam containing a silicon atom in the B ring was prepared starting from allyldimethyl-(chloromethyl)-silane. The simple 6-unsubstituted structure did not show any relevant antibiotic activity, but it represents the first example of the synthesis of a molecule with a structure of a "sila-cephem".*

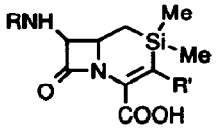
The structural variation of the skeleton of naturally occurring β-lactams, keeping the β-lactam functionality intact, is a possible approach to the modification of bio-active structures in the search of new more potent and specific antibiotics.[2] The B ring of cephalosporins is a suitable structure to perform such variations. Isosteric and non-isosteric modifications of the original structure of cephalosporin-C (**1**) has been attempted giving different and sometimes encouraging results in terms of microbiological activity.[3]



1: R = D-5-aminoadipyl-; R' = CH_2OAc



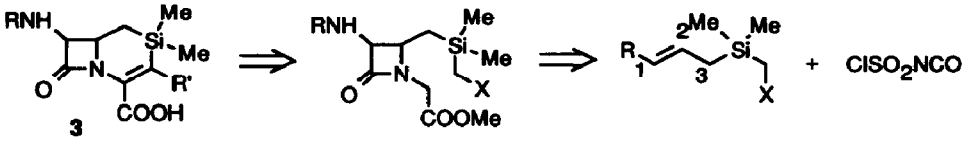
2: X = S, O, CH_2, $PO(OR)_2$; Y = CH_2, S, O.



3

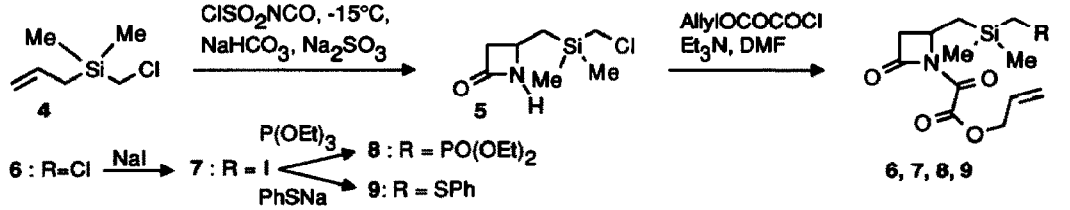
Following our interest in the synthesis of silylated compounds as synthetic tools for organic synthesis[4] and as bio-organosilanes,[5] we became interested in the synthesis of a 2-sila-1-carbacephem (**3**). We report here our approach to this structure with the solution of the problem of the ring construction.

A retrosynthetic analysis showed a first logical disconnection on the double bond in position 3 followed by the closure of the β-lactam ring using the cycloaddition of a substituted allylsilane and chlorosulfonyl isocyanate.



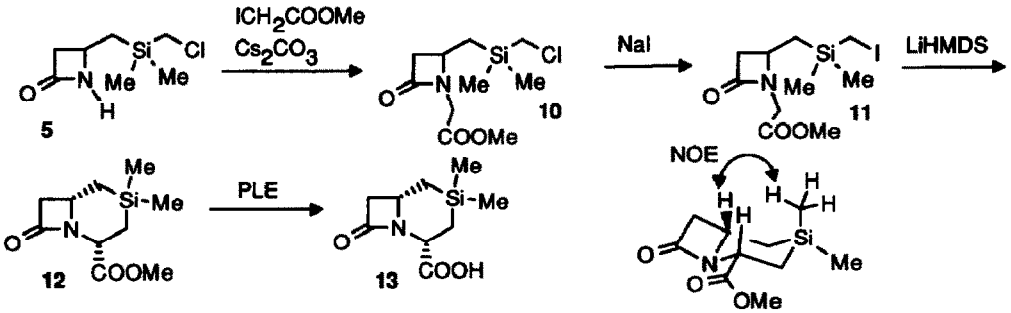
Allylsilanes having an heteroatom or a function which could be transformed into a NHR group in position 1, proved to be extremely difficult to prepare, so that we decided to carry over the reaction on allyl-(chloromethyl)-dimethylsilane (**4**).

The β-lactam **5** was obtained in 78% yield by carrying out the reaction in CCl_4 at -15°C for 18 h, followed by the addition, at the same temperature, of the mixture of Na_2SO_3, $NaHCO_3$ and water.[6] After acylation of the 1H-azetidinone **5** with allyloxalyl chloride (AllylOCOCOCl, DMF, Et_3N, -15°C for 6 h 56% yield), we performed the exchange of the chlorine with iodine (NaI, acetone, r.t., 24 h, 89% yield) and transformed the iodo **7** derivative into the phosphonate **8** (triethylphosphite, 140°C, 2 h, 66% yield).



The intramolecular Horner-Emmons reaction on product **8** was attempted using different reaction conditions but did not give any positive result. Analogously we were not able to generate the carbanion on the $SiCH_2SPh$ group of **9** (prepared from **7** with PhSNa in DMF, 47% yield) which was supposed to react with the carbonyl group.

The ring closure was performed changing the polarity of the new Carbon-Carbon bond formation. Alkylation of 1H-azetidinone (**5**) was performed with iodomethyl acetate (ICH_2COOMe, Cs_2CO_3, CH_3CN, r.t 24 h, 76% yield) to give product **10**. After chlorine-iodine exchange the ring closure was realised with LiHMDS in THF at -78°C for 2 h to give the structure of the 2-sila-1-carbacephem (**12**) in 75% yield.



Product **25** was isolated as a single diastereoisomer and its structure was determined via a NOE experiment. The deprotection of the methyl ester was performed using PLE (*pig liver esterase*, phosphate buffer, pH 7, acetone, 12 h) to give the free acid **25** in 55% yield. The acid itself was tested for its microbiological activity but (as expected) was inactive.

Nevertheless, we have demonstrated that a bicyclic β-lactam struture can be built choosing a precise retrosynthetic analysis. Further work is in progress to prepare the product with the required functionality (Nitrogen at C-6) for the evaluation of the biological activity.

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