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# A SYNTHESIS OF ANTIBIOTIC (±)-PS-5.

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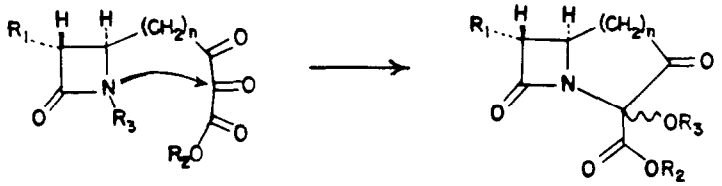
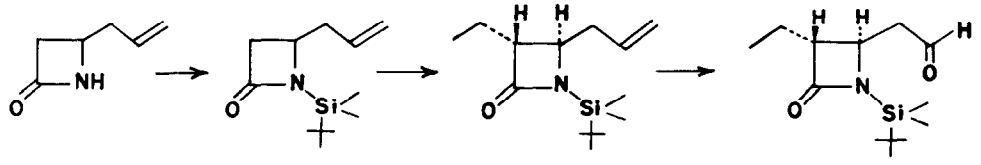
Abstract: A novel method for the formation of antibiotic (±)-PS-5 is described, involving intramolecular cyclization of a β-lactam with a tricarbonyl residue. This procedure represents another application of the enamine-singlet oxygen reaction in synthesis.

In a previous communication [1] we described a procedure for generating vicinal tricarbonyl systems of structure 1 (n=2) which, on cyclization, could yield carbacepham derivatives (2, n=2). We now report the application of this method to the formation of carbapenams, and, in particular, for the synthesis of antibiotic PS-5.



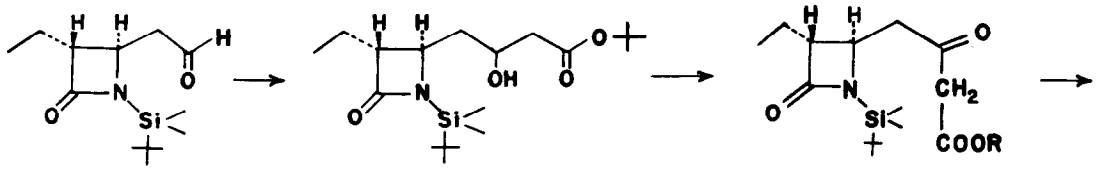
1 2

As the starting point in our synthesis, we employed 4-allylazetidinone (3)[2] (Scheme I). Conversion of 3 to the N-t-butyldimethylsilyl derivative (4)(t-BuSiMe$_2$Cl, Et$_3$N, DMF, 93%) was followed by alkylation using ethyl iodide (LDA, HMPA, THF, -78°C) to form (5)(90%).[3] Ozonolysis of (5)($CH_2Cl_2$, -78°C) followed by reductive workup using dimethyl sulfide yielded (6)(73%) which was then condensed with the lithium enolate of t-butyl acetate to form the β-hydroxy ester (7)(97%). PCC oxidation of (7) yielded the β-keto ester (8a)(70%).

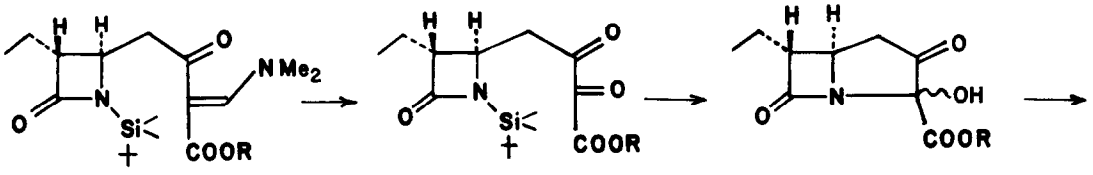


3 4 5 6

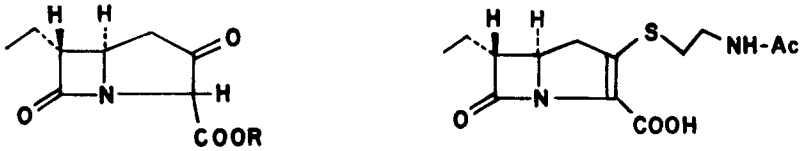
Scheme I



6 7 8a, R=tBu 8b, R=PNB



9a, R=tBu 9b, R=PNB 10a, R=tBu 10b, R=PNB 11a, R=tBu 11b, R=PNB

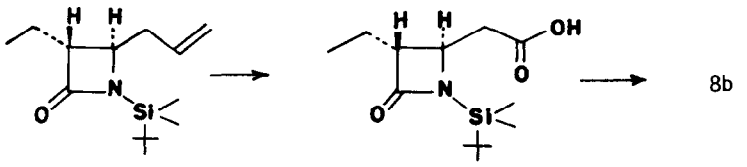


12a, R=tBu 12b, R=PNB 14

Scheme II

As in our earlier study directed toward the carbacepham nucleus, the active methylene group in compound (8a) was converted to an enamino function (9a) ($(CH_3)_2NHCH(OCH_3)_2$) (87%), and this product was subjected to photooxidative cleavage (8 h). The diketo ester formed in the singlet oxygen reaction (10a)(92%) was purified by silica gel flash chromatography.[4] The NMR and IR spectra showed that it was hydrated. Treatment of (10a) with HF-pyridine complex in $CH_3CN$ yielded the desilylated, hydrated tricarbonyl derivative which underwent cyclization in the presence of molecular sieves to (11a). The somewhat labile 11a (84%) was reduced without further purification by conversion of the hydroxyl group to the chloride ($SOCl_2$,pyridine,THF) followed by treatment with Zn in acetic acid to afford (12a)(42%).[5] (Scheme II)

In the synthesis directed toward the antibiotic (±)-PS-5, the allyl derivative (5) was subjected to oxidative cleavage using $NaIO_4$ in the presence of a catalytic amount of $RuCl_3 \cdot 3H_2O$($CH_3CN/CCl_4/H_2O$;1:1:2)[6] to yield (13)(89%)(Scheme III). The extension of the side chain at the 4-position of (13) in the reaction sequence leading to (8b) was accomplished by activation of the acid with carbonyldiimidazole followed by treatment with the magnesium salt of the mono-p-nitrobenzyl ester of malonic acid (68%).[7] By a series of transformations similar to those described above for the formation of (12a) from (8a),




5 13 Scheme III

compound (8b) was converted to (9b) (89%) and then to (10b) (hydrated) (42%).[8] Compound (10b) was then desilylated with HF-pyridine, and, in the presence of molecular sieves, converted to the carbinol amide (11b). This product (93%) was then directly reduced by trimethylsilyl iodide (2.3 eq., -40 to -20°C, $CH_2Cl_2$)[9] to the carbapenam ester (12b)(30%) which was shown to be identical (NMR, IR, mass spec.) to the p-nitrobenzyl ester intermediate prepared by the method of Kametani.[10] Kametani has converted (12b) to the p-nitrobenzyl ester derivative of (±)-PS-5, while more recently, Favara has synthesized (12b) in chiral form and has converted it to (+)-PS-5 (14).[11] Our reaction sequence thus constitutes a formal total synthesis of antibiotic PS-5 in racemic form. We are giving further study to the use of vicinal tricarbonyl systems for the formation of penam and penem derivatives.

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## References


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4. Ozonolysis of 9a in methylene chloride at -78°C also gave 10a(54%).

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8. The singlet oxygen reaction with 9b required ca. 2 1/2 days. The longer reaction time may be associated with the presence of the electronegative PNB group. Some of the acid (13) (14%) was also formed concurrently. Ozonolysis of 9b yielded 10b (38%).

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