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TOTAL SYNTHESIS OF (±)-CLAVAM-2-CARBOXYLIC ACID

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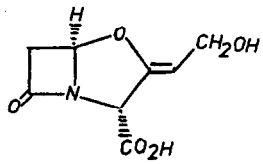
SUMMARY: Racemic clavam-2-carboxylic acid has been obtained by a six-step synthesis from readily available starting materials.

Clavulanic acid (1), a highly potent, broad spectrum and irreversible ß-lactamase inhibitor[1] with clinical applications[2], was isolated from fermentation of the microorganism Streptomyces clavuligerus[3]. The remarkable capability of this Streptomyces to elaborate a plethora of ß-lactam antibiotics[1] in penicillin, cephalosporin and clavam families, has prompted much investigation in this area. Thus, certain ß-lactams structurally related to clavulanic acid, lacking the C-3 carboxyl group, have been recently isolated from this organism[4]: 2a (R=COOH), 2b (R=CH_2OH), 2c (R:CH_2OCHO) and 2d (R=$CH_2CH(NH_2)COOH$); which have been found to show antifungal activity against a variety of animal and plant pathogens[5].



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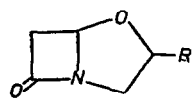
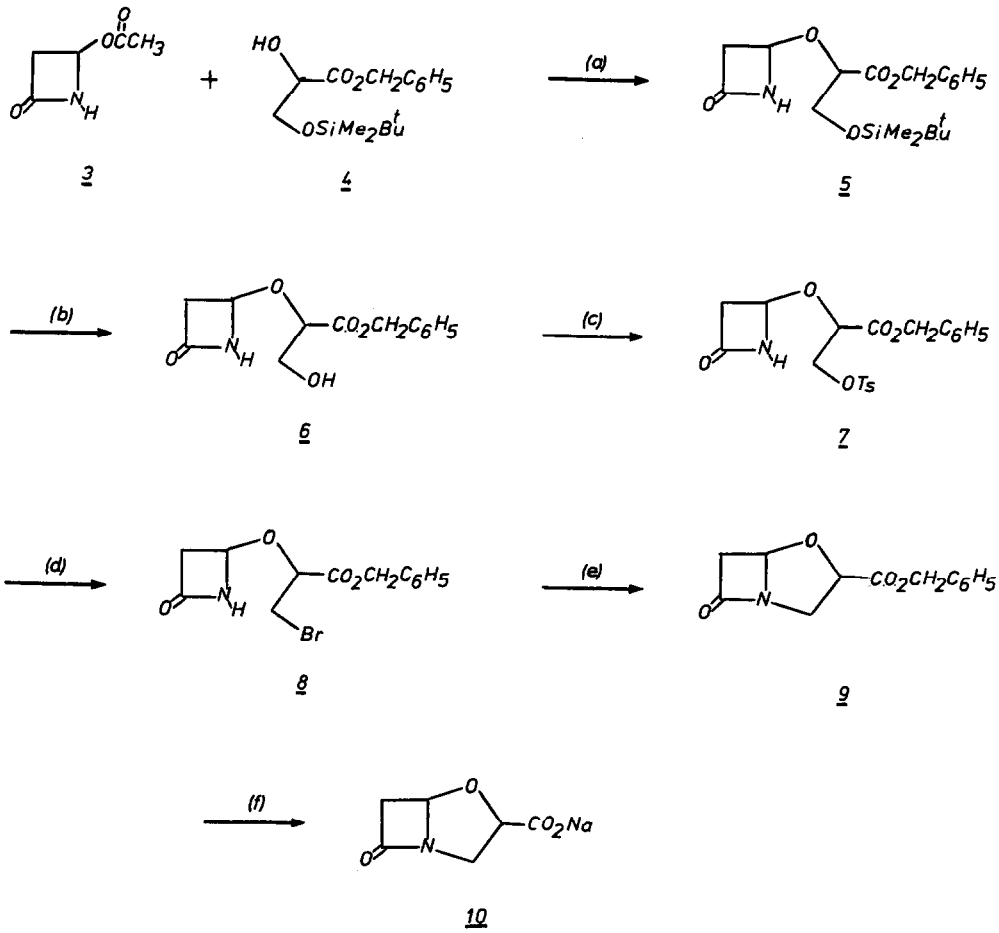


2

Most of these metabolites and other clavam derivatives without a carboxyl function at C-3 have been prepared by total synthesis[6], however, the synthesis of clavam-2-carboxylic acid (2a) has not been described yet.

SCHEME 1



a) $(AcO)_2Pd$ / bencene / Et_3N
b) CH_3CO_2H /THF/ H_2O
c) ClTs / pyridine
d) LiBr / HMPA
e) FOD-Ag / DMF
f) H_2 /Pd-C / $NaHCO_3$

Ts = p-toluenesulfonyl

We now wish to report a procedure for the total synthesis of the title compound. The method is based on the use of the ß-lactam 3 and the propanoic acid derivative 4, both easily available, as starting materials and the C-3 to N closure by using a silver complex, as key-step for the construction of the oxapenam ring system. The sequence is outlined in scheme 1[7].

Condensation of the racemic glyceric acid derivative 4, appropriately protected at the primary hydroxyl group, with 4-acetoxy-2-azetidinone (3)[8], at room temperature, in benzene, in the presence of triethylamine (1 equivalent) and using palladium acetate as catalyst gave, after silica gel chromatography, the ß-lactam 5 in 63% yield. After deprotection of 5 under acidic conditions (3:1:1 acetic acid-water-tetrahydrofuran), the corresponding alcohol 6 (m.p: 130-1°) was obtained. Reaction of 6 with p-toluenesulfonyl chloride in pyridine afforded the tosylate 7 (92% yield; m.p: 104-5°) which by treatment with lithium bromide in hexamethylphosphoramide yielded quantitatively the corresponding bromide 8 (m.p: 84-6°). Cyclisation by intramolecular N-alkylation of 8 with silver 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionate (FOD-Ag)[9] in dimethylformamide at room temperature, followed by chromatography, led to the formation of a racemic mixture of clavam 9 in 20% yield. Hydrogenolysis of the corresponding benzyl ester 9 in the presence of one equivalent of sodium hydrogen carbonate, gave the desired sodium clavam-2-carboxylate (10) in almost quantitative yield.

Other important aspects of this work such as separation and assignment of diastereoisomers as well as biological activity, are currently under investigation.

ACKNOWLEDGMENTS. We thank Mr. Raúl Fernández for skilfull technical assistance.

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7. All new compounds are racemic mixture of diastereoisomers and they have spectroscopic and elemental and/or mass spectral data in accord with structures indicated.

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9. FOD-Ag is a commercially available, soluble silver complex.

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