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A TOTAL SYNTHESIS OF 6-METHOXY-*epi* PS-5 FROM AMINOMALONATE.

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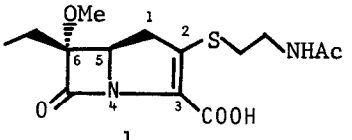
ABSTRACT : 6-Methoxy-*epi* PS-5 1 was stereoselectively synthesized *via* a bicyclic β-lactam from N-benzyloxycarbonylaminomalonate.

Although many members of the carbapenem family have been isolated from microorganisms, N-formimidoylthienamycin[1] in combination with cilastatin, a synthetic inhibitor of renal dehydropeptidase I, is the sole semi-synthetic carbapenem drug which is available for clinical use in Europe, because naturally occurring analogs are unexpectedly sensitive to the dipeptidase. In a synthetic approach to this problem, we have developed a versatile method for modification of the sulfur side chain at C-2 of PS-5[2] and synthesized a variety of PS-5 derivatives. To date we have not yet obtained a PS-5 derivative which is sufficiently resistant to dehydropeptidase I without an inhibitor. Based on the hitherto collected information that the 7-methoxy group in cephamycin analogs serves to improve resistance to β-lactamases, we have planned to synthesize 6-methoxy-PS-5 and determine the comparative antimicrobial activities and dehydropeptidase I stabilities of PS-5 and its 6-methoxy derivative, in expectation of satisfactory resistance of the latter to the dipeptidase. This report describes a method of stereoselective synthesis of 6-methoxy-*epi* PS-5 1.



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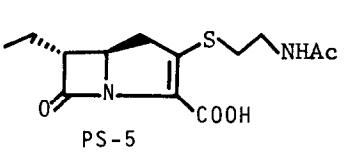
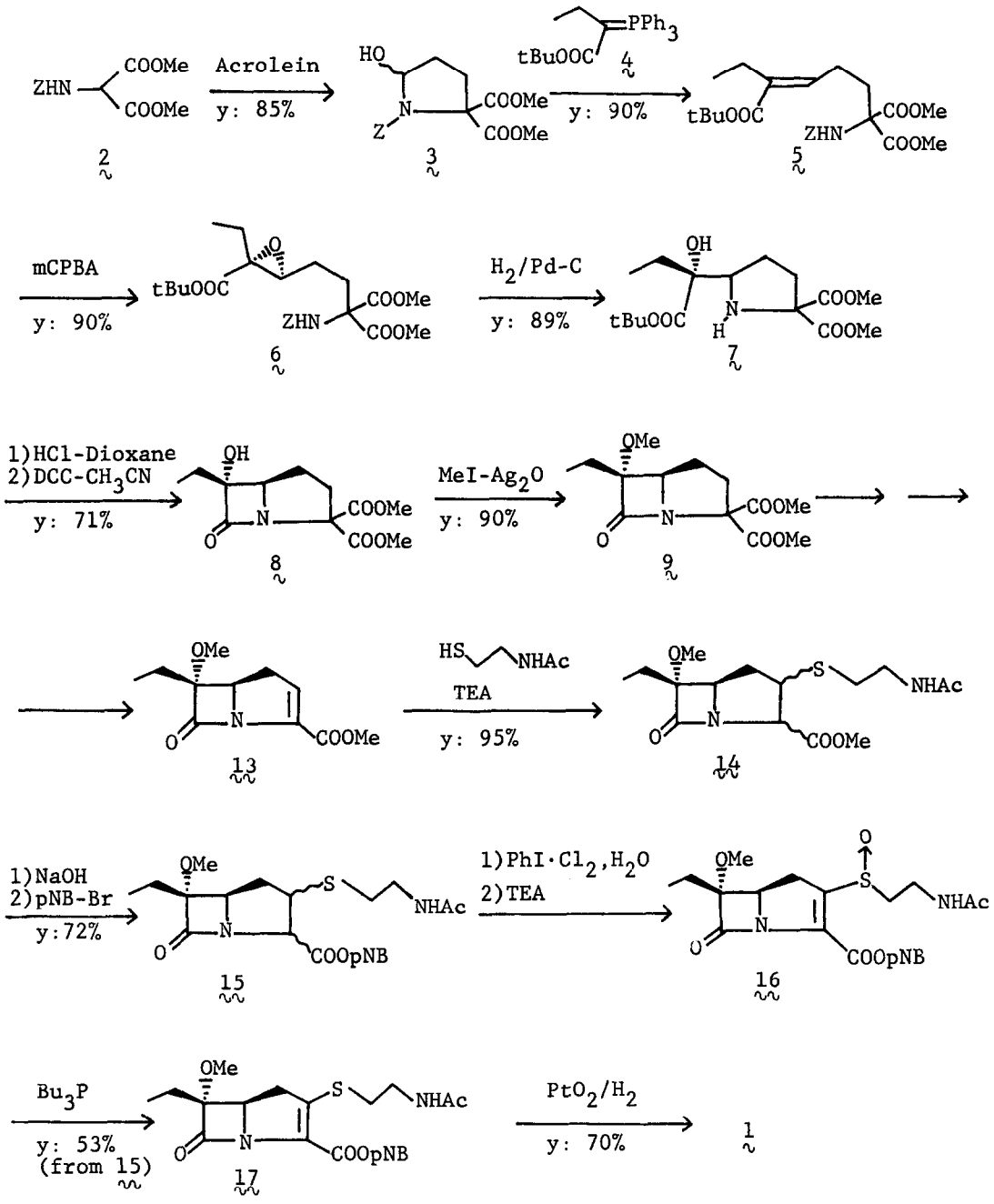
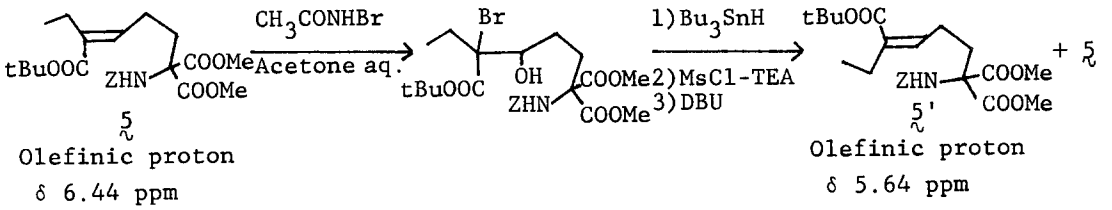


PS-5

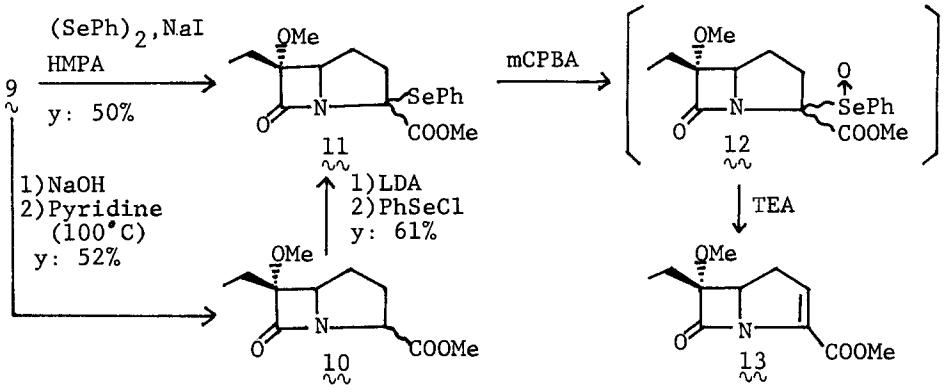
Fig. 1 Scheme of synthesis of 6-Methoxy-epi PS-5



The scheme of total synthesis is outlined in Fig. 1. Dimethyl N-benzyloxycarbonylaminomalonate 2, which is easily obtainable from dimethyl malonate, was employed as starting material. The Michael reaction of 2 with acrolein in the presence of a catalytic amount of sodium methoxide gave a pyrrolidine derivative 3 in 85 % yield. An α,β-unsaturated ester 5 was predominantly provided by the Wittig reaction of 3 and α-tert-butoxycarbonylpropylidenetriphenylphosphorane 4. The geometrical isomerism of trans in 5 was confirmed by spectroscopic comparison of the olefinic proton[3] in the ^{1}H-NMR spectra of 5 and its isomer 5' prepared as shown below.



Epoxidation of 5 with m-chloroperbenzoic acid in methylene chloride at 40°C for 4 hours afforded an epoxide 6 in 90 % yield. Deprotection of the epoxide 6 led to a pyrrolidine derivative 7 at room temperature in 89 % yield. A bicyclic β-lactam 8 (yield 71 %) was obtained by treatment of 7 with hydrochloric acid and then with dicyclohexylcarbodiimide in acetonitrile. Methylation of 8 with methyliodide in the presence of silver oxide gave a methoxy carbapenam 9 in 90 % yield. The carbapenam 9 was converted to 6-methoxycarbapenem 13 as follows:



In the first trial, 9 was hydrolysed in sodium hydroxide and then heated to give a diastereoisomeric mixture of a decarbomethoxy compound 10. 10 was treated with lithium diisopropylamide, and successively with phenylselenyl chloride to produce a phenylselenyl derivative 11 (yield 61 %). Derivative 11 was later found to be obtained in a better yield directly from 9 by the method of Asaoka et al.[4] More particularly, in the presence of two moles of sodium iodide and one mole of diphenyldiselenide, one mole of 9 in hexamethylphosphorictriamide was heated at 80°C for 2 hours to give 11 in 50 %

yield together with unreacted 9 (in 30 % amount). The resulting selenide 11 was transformed to the carbapenem 13 in good yield via a selefinyl intermediate 12 which could be easily β-eliminated. Addition reaction of N-acetylcysteamine to the carbapenem 13 by the method of Bateson et al.[5] led to a diastereoisomeric mixture of a compound 14 in good yield. The ratio of the three diastereoisomers [(2α,3β):(2β,3α):(2β,3β)] was determined to be 2:5:3 by comparison of the chemical shifts of the C-3 proton in the proton NMR spectrum.[6] Compound 15 was yielded from 14 by ester group exchange and was led to a sulfinyl compound 16.[7] Treatment of 16 with tributylphosphine afforded an ester 17 (yield from 15 : 53 %), which was hydrogenated in a usual way, resulting in the title compound 1 in 70 % yield. The NMR, UV and IR spectral data[8] support the proposed structure for 1.

As expected, the renal dehydropeptidase I stability of 1 was very significantly improved by introduction of the methoxy group at C-6 and seemed to be satisfactory for clinical use. The comparative antimicrobial data of PS-5 and 1, however, showed that the former was antimicrobially about 20 - 40-fold more active than the latter (for example, MIC of 1 was 0.78 μg/ml against Staphylococcus aureus 209P and 25 μg/ml against Escherichia coli K-12 while MIC of PS-5 was 0.024 and 1.56 μg/ml, respectively).

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6. Chemical shift data : δ 4.33 (J=6.0 Hz) for (2α,3β); δ 4.19 (J=8.0 Hz) for (2β,3α); δ 4.72 (J=8.0 Hz) for (2β,3β).
7. H.J. Bateson, P.M. Roberts, T.C. Smale and R. Southgate: J. Chem. Soc., Chem. Commun. 185 (1980).
8. Spectral data of 1 (sodium salt) : $\lambda_{max}^{H_2O}$nm(ε) 305.5 (8,000); $\nu_{max}^{KBr}cm^{-1}$ 1752 (β-lactam), 1665 (amide), 1608 (carboxylate); ^{1}H-NMR (D_2O, DSS) δ 0.96 (3H,t,J=7.5 Hz,$CH_2\underline{CH_3}$), 1.87 (2H,q,J=7.5 Hz,$\underline{CH_2}CH_3$), 1.97 (3H,s,$COCH_3$), 2.70-3.50 (6H,m,C-$1H_2$,S-$CH_2\underline{CH_2}$N), 3.50 (3H,s,OCH_3); ^{13}C-NMR (D_2O, dioxane) δ 177.1 (s), 175.2 (s), 168.5 (s), 130.8 (s), 128.3 (s), 92.6 (s,C-6), 60.4 (q,OCH_3),54.2 (d,C-5), 40.4 (t), 35.8 (t), 31.7 (t), 23.9 (t), 22.8 (q), 7.1 (q).

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