PENICILLIN-CEPHALOSPORIN CONVERSION WITH COMPLEATE UTILIZATION OF ALL THE FRAMEWORK ELEMENTS

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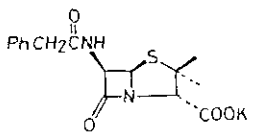
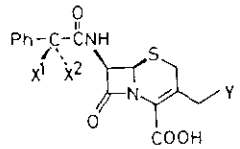
Recently, successful conversion of penicillins to useful cephalosporin antibiotics has been developed by several groups. In the final stage, the C(7)-acylamino groups, derived from the C(6)-substituents of natural penicillins, have been replaced with the desired acylamino groups. On the other hand, some of cephalosporins of newer generation, e.g., 1a-c, possess α-substituted phenacylamino groups at the C(7)-position.



Pc-G



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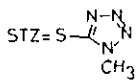
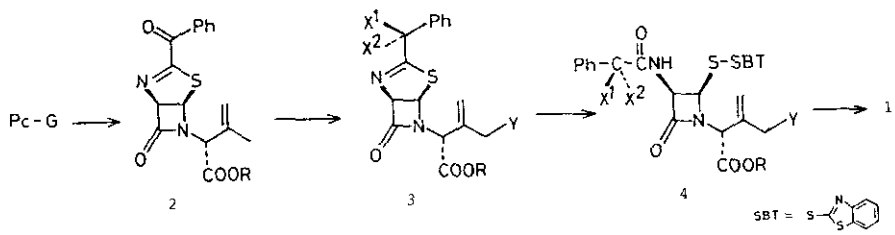


		R	Y
a	Cefamandole	PhC(H)(OH)-	STZ
b	SKF-80000	PhC(=NOH)-	STZ
c	Lafarguim AL-726	PhC(H)(OH)-	H

This paper describes an efficient synthesis of cephalosporins 1a-c from penicillin G without discarding any of the framework elements as outlined in the following scheme.

Thiazoline-azetidinones 3 ($C^{X^1}_{X^2}$ = C=O; Y = Cl) were obtained by the electrolytic ene-type chlorination of thiazoline-azetidinones 2 derived from penicillin G [Tetrahedron Lett., 22, 3193 (1981)]. Replacement of the allylic chlorine atom with STZ was performed by two-step operation: NaI/acetone (Δ); NaSTZ/acetone. Reduction of 3 ($C^{X^1}_{X^2}$ = C=O; Y = STZ) with Zn/AcOH/CH_2Cl_2, BH_3NH_3/CH_2Cl_2, or $+e^-$ afforded the corresponding alcohols 3 (X^1= H, X^2= OH/ X^1= OH/X^2= H: 3/2 1/2). Transformation of 3 to dithioazetidinones 4 was achieved by the hydrolytic ring-opening of the thiazoline moiety and simultaneous trapping of the thiol group with BTS→ in aq. HCl/THF. Cyclization of 4 with NH_3/DMF and/or modification of the benzylic C=O group yielded 1a-c, respectively.



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