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A NOVEL APPROACH TO DEACYLATION OF CEPH-3-EM ESTERS

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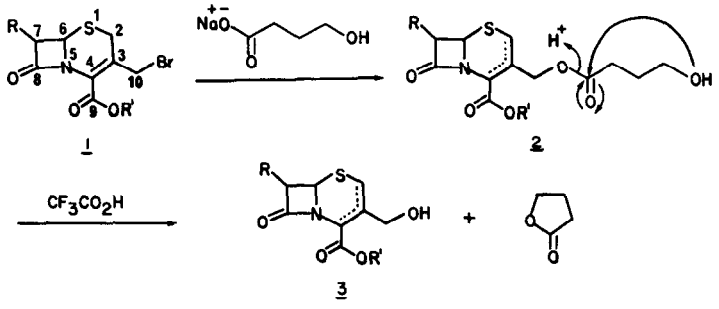
Abstract: A new method for the preparation of cephalosporin C-10 alcohols from C-10 esters is described. The approach involves formation of an intermediate iodocephem 5, conversion of 5 to the trifluoroacetyl ester 6, and hydrolysis of 6 in phosphate buffer to afford 7 as a single product.

Semisynthetic manipulation of the cephalosporin nucleus frequently requires the preparation of C-10 deacetyl cephems (e.g., 7),[1,2] compounds that are often not easily obtained. The β-lactam ring of cephalosporins is exceptionally labile to both acids and bases, which may account for the fact that there are very few chemical methods reported for cephem deacylation. The treatment, for example, of cephalothin (4, R' = H) with base effects removal of the C-10 acetyl group, but ester hydrolysis is invariably accompanied by cleavage of the β-lactam ring and by lactonization.[3] Hydrolytic cleavage of cephem C-10 esters under acidic conditions is similarly accompanied by undesired side reactions, and the necessarily extensive product purifications usually afford the desired C-10 alcohols in low yield.[4]

A unique, if perhaps circuitous, route to cephem C-10 alcohols is provided by Koppel and Nummy.[5] They obtained the ester 2 by reaction of the bromocephem 1---which is first prepared from a penicillin---with γ-hydroxybutyrate. Treatment of 2 with trifluoroacetic acid gives intramolecular lactonization, affording 3. Initial formation of 2, however, proceeds with $\Delta^3 \rightarrow \Delta^2$ isomerization of the cephalosporin, and, consequently, 3 is a mixture of Δ^3- and Δ^2-isomers.

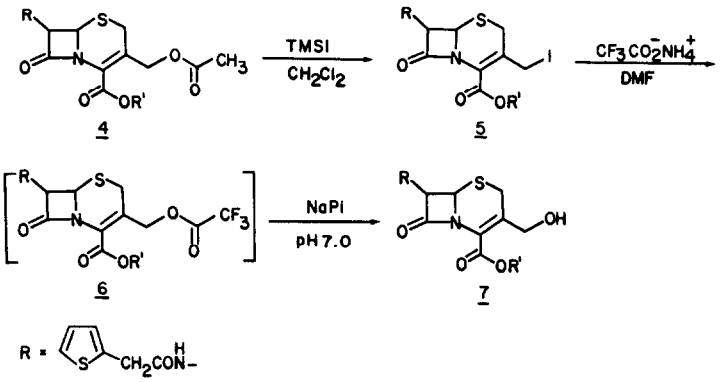


1 2 3

Subsequent isomeric resolution[6] to obtain the desired Δ^3-cephem alcohol further complicates an already multistep preparation and compromises the yield.

A number of groups have made use of citrus acetyl esterase[2a] for cephem deacylation, as first described by Jansen and Jang.[7] Esterases from the genera Actinomycetes,[1b] Schizomycetes,[2b] Rhizobium,[2c] and Rhodotorula,[2d] and from the bacterium Bacillus subtilis[2e] have also been found useful for preparation of cephalosporins such as 7 (R' = H), which subsequently are esterified at C-9. Enzymatic methods for cephem deacylations are more conveniently accessible to the synthetic chemist now that the citrus acetyl esterase and the B. subtilus enzyme have become commercially available. But neither enzyme has an especially high specific activity for reaction with cephalosporins, and large quantities of protein are often required to assure isolation of cephem C-10 alcohols in high yield.

During the course of preparing cephalosporins that incorporate antibacterial peptides as C-10 esters,[3b,8] we discovered a facile chemical method for deacylation of cephems that can be carried out under essentially neutral conditions and affords compounds such as 7 in high yields. We find that the carboxyl-protected derivative of cephalothin 4 (R' = p-nitrobenzyl), prepared as described elsewhere,[9] reacts with iodotrimethylsilane to give the C-10 iodocephem 5.[10] Reaction of the iodide with trifluoroacetate affords the unstable ester 6. We do not attempt to isolate 6, but hydrolyze it in situ by the addition of 100 mM sodium phosphate buffer, pH 7, which gives the desired cephem 7 in excellent yield.[11]



4 → 5 → 6 → 7

By contrast to 1 → 3, our method 4 → 7 proceeds without isomerization of the Δ^3-cephem, probably because trifluoroacetate is a relatively poor base. Correspondingly, trifluoroacetate is a relatively weak nucleophile, which may account for its somewhat sluggish reaction with 5; typically, this esterification is carried out at 50°C for 45 min. The sequence 5 → 7 is conducted using scrupulously dried DMF so to avoid premature hydrolysis of 6 and, consequently, the potential lactonization of 7. Nonetheless, a small amount of lactone (~4%) is formed during

work-up, but this can be removed by subsequent recrystallization. We have obtained the trichloroethyl cognate of 7 by the same sequence that gave the nitrobenzylated compound. It would seem that this route will have general applicability for deacylation of a variety of C-10 cephem esters, providing a practical chemical approach to the preparation of these useful synthetic intermediates.

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10. The ester 4 (5.0 g, 9.4 mmol) was dissolved in 50 mL dry CH_2Cl_2 and reacted with TMSI (2.0 mL, 14.1 mmol) in the dark under N_2 at room temperature. After 1.5 h, the solution was washed with 10% $Na_2S_2O_3$, water, 10% $NaHCO_3$ and water and then dried over $MgSO_4$. The filtrate was concentrated to 20 mL and chilled in an ice-bath. Hexane (~300 mL) was added over 45 min to crystallize the product. After filtration and air drying, 4.65 g of a pale-yellow solid was recovered. Yield, 82%; mp 142-145°C (dec.); IR ($CHCl_3$): 1792, 1729, 1652, 1336, 1112 cm^{-1}; R_f 0.52 (3:1, benzene/ethyl acetate); ^1H NMR ($CDCl_3$): δ 3.48, 3.76 (2d, 2H, C-2, J = 18.1 Hz), 3.85 (s, 2H, side-chain methylene), 4.37 (s, 2H, C-10), 3.96 (d, 1H, C-6, J = 5.0 Hz), 5.29, 5.37 (2d, 2H, benzylic, J = 13.1 Hz), 5.80 (m, 1H, C-7), 6.22 (d, 1H, NH-side chain, J = 9.0 Hz), 7.00 (m, 2H, thienyl), 7.26 (m, 1H, thienyl), 7.56, 8.20 (2d, 4H, phenyl, J = 8.6 Hz); anal. ($C_{21}H_{18}N_3O_6S_2I$) C, H, N, I.

11. A solution of the iodide 5 (1.5 g, 2.5 mmol) and ammonium trifluoroacetate (655 mg, 5.0 mmol) in 30 mL dry DMF was stirred at 50°C for 45 min. The reaction was brought to r.t., and a 15 mL aliquot of 100 mM sodium phosphate buffer, pH 7.0, was added, followed by stirring at r.t. for 15 min. The solution was poured into a mixture of EtOAc and sat. $CaCl_2$. The organic layer was washed with sat. $CaCl_2$ (2x), water, dried over $MgSO_4$ and evaporated to dryness; the residue was dissolved in 10-15 mL of CH_2Cl_2 and filtered. To the filtrate was added ~150 mL of hexane, from which 1.02 g of 7 crystallized. Yield, 83%; sintered, >90°, melted 103-109°C (dec.); IR ($CHCl_3$): 3300, 1795, 1724, 1689 cm^{-1}. R_f 0.56 (1:1, benzene/ethyl acetate); ^1H NMR ($CDCl_3$): δ 2.48 (br s, 1H, OH), 3.58 (s, 2H, C-2), 3.85 (s, 2H, side-chain methylene), 4.03, 4.46 (2d, 2H, C-10, J = 13.0 Hz), 4.93 (d, 1H, C-6, J = 5.0 Hz), 5.28 (2d, 2H, benzylic, J = 13.0 Hz), 5.84 (m, 1H, C-7), 6.24 (d, 1H, NH-side chain, J = 8.7 Hz), 6.99 (m, 2H, thienyl), 7.25 (m, 1H, thienyl), 7.55, 8.20 (2d, 4H, phenyl, J = 8.6 Hz); anal. ($C_{21}H_{19}N_3O_7S_2$) C, H, N.

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