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AN IMPROVED ENTRY TO A KEY INTERMEDIATE FOR THIENAMYCIN SYNTHESIS FROM METHYL (R)-3-HYDROXYBUTANOATE VIA DIRECT EPIMERIZATION AT C-3 ON 2-AZETIDINONE RINGS

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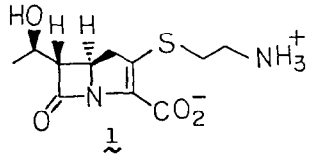
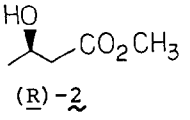
Summary: An improved entry to a key thienamycin intermediate is described which relies upon the direct epimerization at C-3 of the 3-(1-hydroxyethyl)-2-azetidinone derivatives readily obtained from methyl (R)-3-hydroxybutanoate.

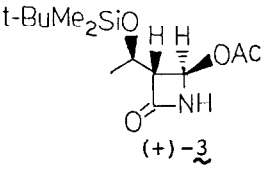
Thienamycin (1) has been the focus of current synthetic attention.[2] Recently we have reported a synthetic route to the key thienamycin intermediate (3) based on the enolate-imine condensation of methyl (R)-3-hydroxybutanoate (2) with the N-silylimine generated in situ from trimethylsilylpropynal (Scheme 1, Route A).[3] Since the major condensation product (4) possesses the wrong configuration at C-3, the most crucial operation in this route is the transformation of 4 to the 3-epimeric derivative (6) which has required the tedious, five-step sequence including reduction of ketone 5 that was not highly stereoselective.[4] Herein we report a more efficient by-pass to 6 which relies on the direct epimerization at C-3 via the lactam silyl enol ether 7 (Route B).



1

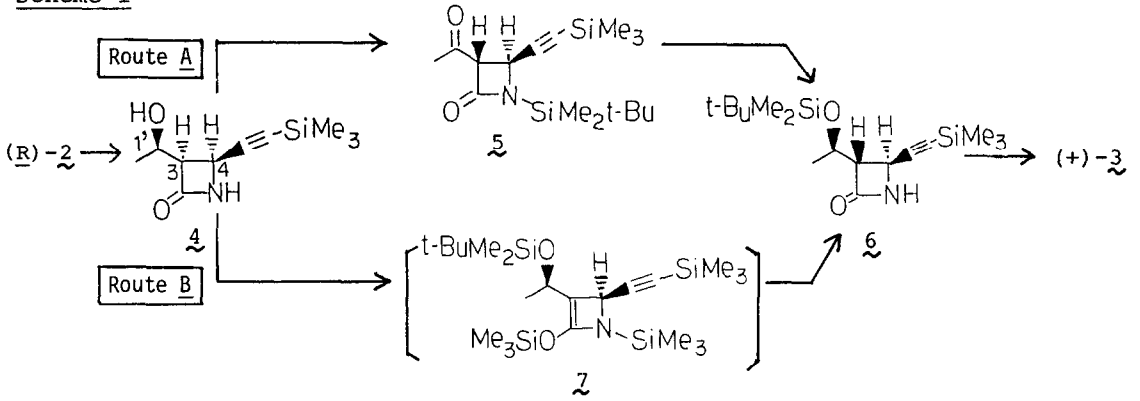


(R)-2



(+)-3

Scheme 1



The newly developed epimerization procedure involves only two steps, i.e., the selective O-silylation of 4 (t-BuMe$_2$SiCl/imidazole)[3] and the further disilylation with trimethylsilyl triflate ($Me_3SiOSO_2CF_3$) leading to the silyl enol ether 7 followed by in situ hydrolysis (aq. HCl). Thus, the O-silylated derivative of 4 was treated with 2.5 equiv. of Me_3SiOTf in the presence of Et_3N (2.5 equiv.) in CH_2Cl_2 at room temperature for two days to afford, after hydrolysis, in 95% isolated yield the epimerized product 6 without any detectable contamination with 4. Hydration of 6 thus obtained followed by the Baeyer-Villiger reaction[3] gave the key intermediate 3 in an extremely high optical purity ($[\alpha]_D^{24}$ +53.7° (c 1.04, $CHCl_3$)), as judged from the highest literature $[\alpha]_D$-value (+50.0 (c 0.41)).[5] Furthermore, we found that a similar epimerization of the N, O-bis(trimethylsilyl) derivative of 4 with Me_3SiOTf was completed over a shorter period (3 h) to afford the unprotected form of 6 in 95% isolated yield.

The complete epimerization at C-3 was indeed a pleasant event since it concurrently establishes the desired (1',3)-syn and (3,4)-trans configuration which are difficult to achieve directly by the enolate-imine condensation.[4,6] The remarkable preference for the β-face protonation is undoubtedly due to the presence of the bulky substituents on C-3 and -4, which direct the entry of proton from β-face leading to the sterically less congested (3,4)-trans configuration, in analogy with the exclusive β-protonation observed during the oxidation of 4 to 5.[3]

In summary, we have described an efficient method for direct epimerization at C-3 of 4, which provides an improved entry to the key thienamycin intermdediate (+)-3 from inexpensive (R)-2 in terms of the higher overall yield, the shorter length of the sequence, and the higher level of stereocontrol. Furthermore, the success of the direct epimerization greatly facilitates the utility of the ethynyl group of 6 as a two-carbon unit for constructing the thienamycin skeleton. Further work along this line is in progress in our laboratory.

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