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A SIMPLE ROUTE TO THE KEY INTERMEDIATE OF 1β-METHYLTHIENAMYCIN

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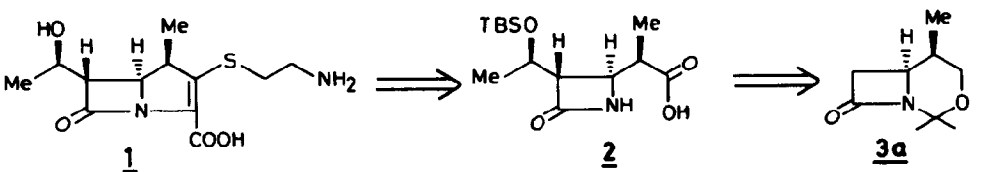
Abstract: A short and straightforward synthetic strategy towards the key intermediate **2** of 1β-methylthienamycin has been described.

1 β-Methylthienamycin (**1**), a totally synthetic analogue of the naturally occurring antibiotic, thienamycin, is being promoted as a viable substitute of thienamycin because of its sustained chemical and metabolic stabilities[1]. The recent synthetic tactics[2] towards **1** or the key intermediates (**2** or **3a**) are now being mobilised in developing such strategies that are capable of producing **1** in large quantities and involve cheap and accessible chemicals. We now report a short and straightforward approach to **3a** and **2**, established[3] intermediates of **1**.



1 **2** **3a**

The commercially available (S)-methyl 3-hydroxy-2-methyl propionate (**4**) whose chiral carbon represented C-1 of **1**, was chosen as a starting material[4]. The derived TBS derivative **5** was reduced with DIBAL-H at -78°C and the resulting aldehyde (**6**) was immediately subjected to two carbon homologation[5] with carbethoxymethylenetriphenylphosphorane (85%). The E-geometry of the newly formed α,β-unsaturated ester **7** was confirmed by ^{1}H-NMR spectrum. Subsequent conjugate addition reaction[6] of **7** with benzylamine in refluxing methanol occurred efficiently giving a chromatographically separable mixture of **8a** and **8b** in the ratio of 7:3 (70%, 90% based on recovered **7**). Both the products were independently transformed into the corresponding β-lactam derivatives. Thus, the faster moving product (**8a**) was hydrogenolysed over Pd-C and subsequently cyclized with tert-butylmagnesium chloride to give the β-lactam derivative (**9a**) (80%). Treatment[2] of **9a** with 1N HCl in methanol followed by isopropylidination with dimethoxypropane-BF_3:OEt_2 resulted in the formation of **3a** $[\alpha]_D$ +37 (c 1.18, $CHCl_3$), lit.[2] +34.6 (c 0.5, $CHCl_3$) in almost quantitative yields. The structure of **3a** was further confirmed unambiguously by the ^{1}H-NMR spectrum in which the characteristic[7] chemical shifts and coupling constants for C_5-methyl, H-4 (axial), H-4 (equitorial) and H-5 (equitorial) were in conformity with the structure.

Transformation of **8b** into the β-lactam derivative **3b** was carried out by successive debenzylation, cyclisation and isopropylidination reactions as described above. The structure of compound **3b**{$[\alpha]_D$ +22 (c 0.8, $CHCl_3$)}was confirmed[8] by the ^{1}H-NMR spectrum (Scheme 1)[9].

Conversion of **3a** into the key intermediate **2** was already demonstrated[2] in these laboratories (Scheme 2).

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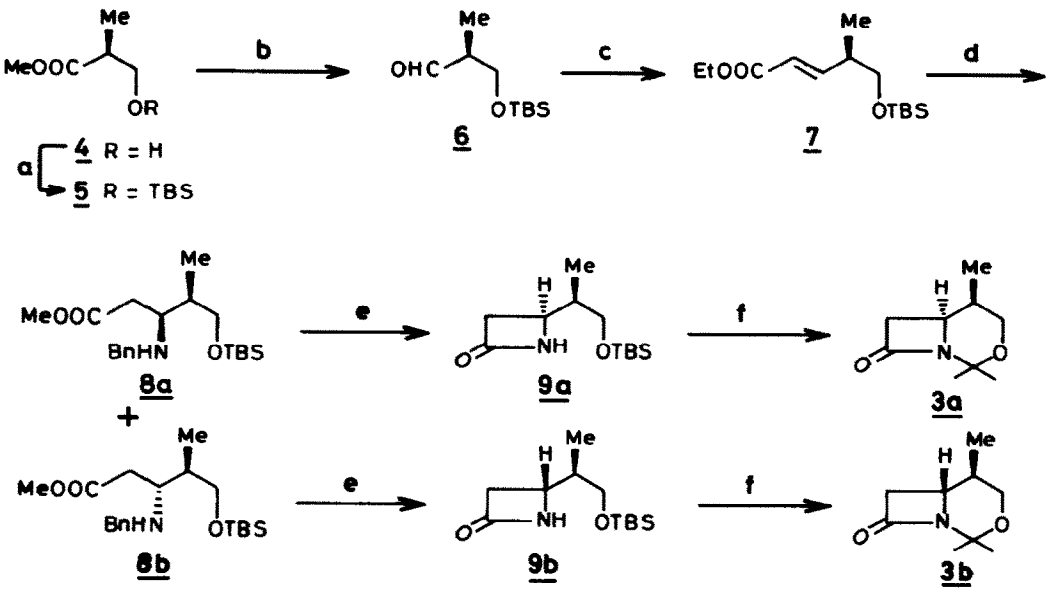
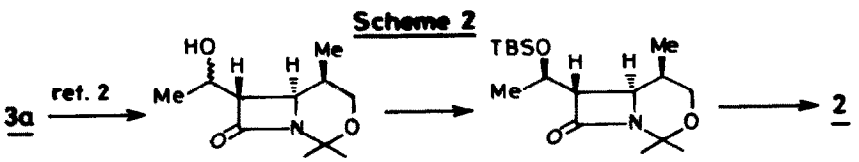
Scheme 1



a) TBS-Cl, imidazole, CH_2Cl_2, 2h; b) DIBAL-H, CH_2Cl_2, -78°C, 15 min; c) $Ph_3P{=}CHCO_2C_2H_5$, CH_2Cl_2, RT, 8h; d) $PhCH_2NH_2$, MeOH, reflux 36h; e) i. Pd-C, MeOH, H_2, 5h; ii. TMS-Cl, Et_3N, ether; iii. t-BuMgCl, ether, RT, 18h; f) i. 1N HCl, MeOH, RT, 1h; ii. $Me_2C(OME)_2$, $BF_3{:}OEt_2$, CH_2Cl_2, 15 min.

Scheme 2



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9. Compound **3b** would be an interesting intermediate to prepare 1 β-methylthienamycin analogue.