AN IMPROVED SYNTHESIS OF AN INTERMEDIATE FOR THIENAMYCIN SYNTHESIS

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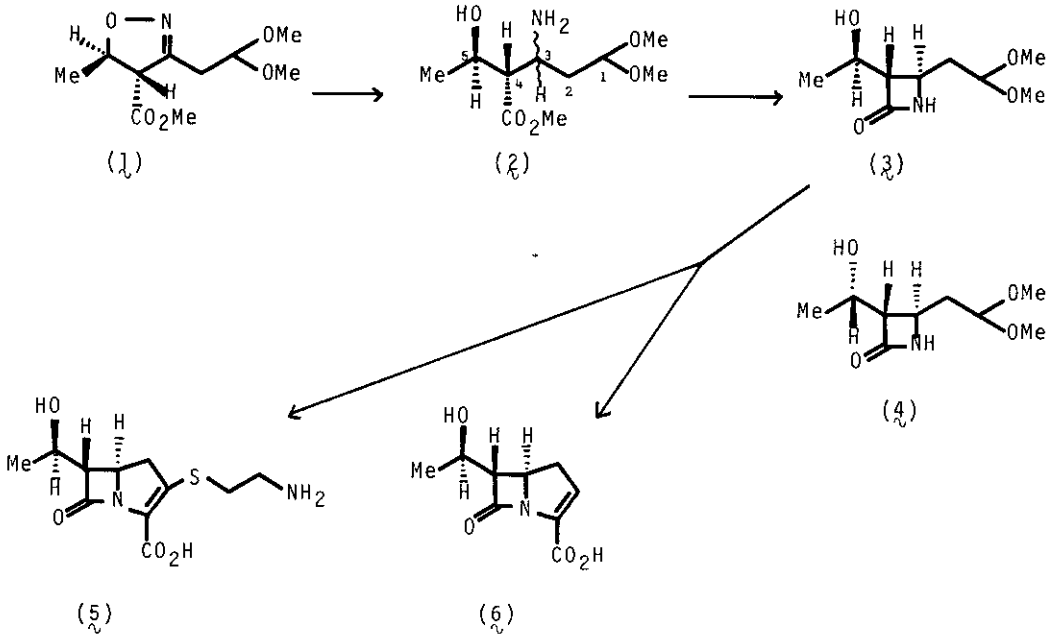
Abstract —— Methyl 3-amino-5-hydroxy-1,1-dimethoxyhexane-4-carboxylate (2) was converted into trans- and cis-azetidinones (3 and 10) by sequential trimethylsilylation, cyclisation with Grignard reagent, and deblocking. The corresponding tert-butyl ester (15), prepared via the isoxazoline derivative (13), was selectively transformed into the trans-β-lactam (3), a synthetic intermediate of thienamycin, by the same reaction sequence.

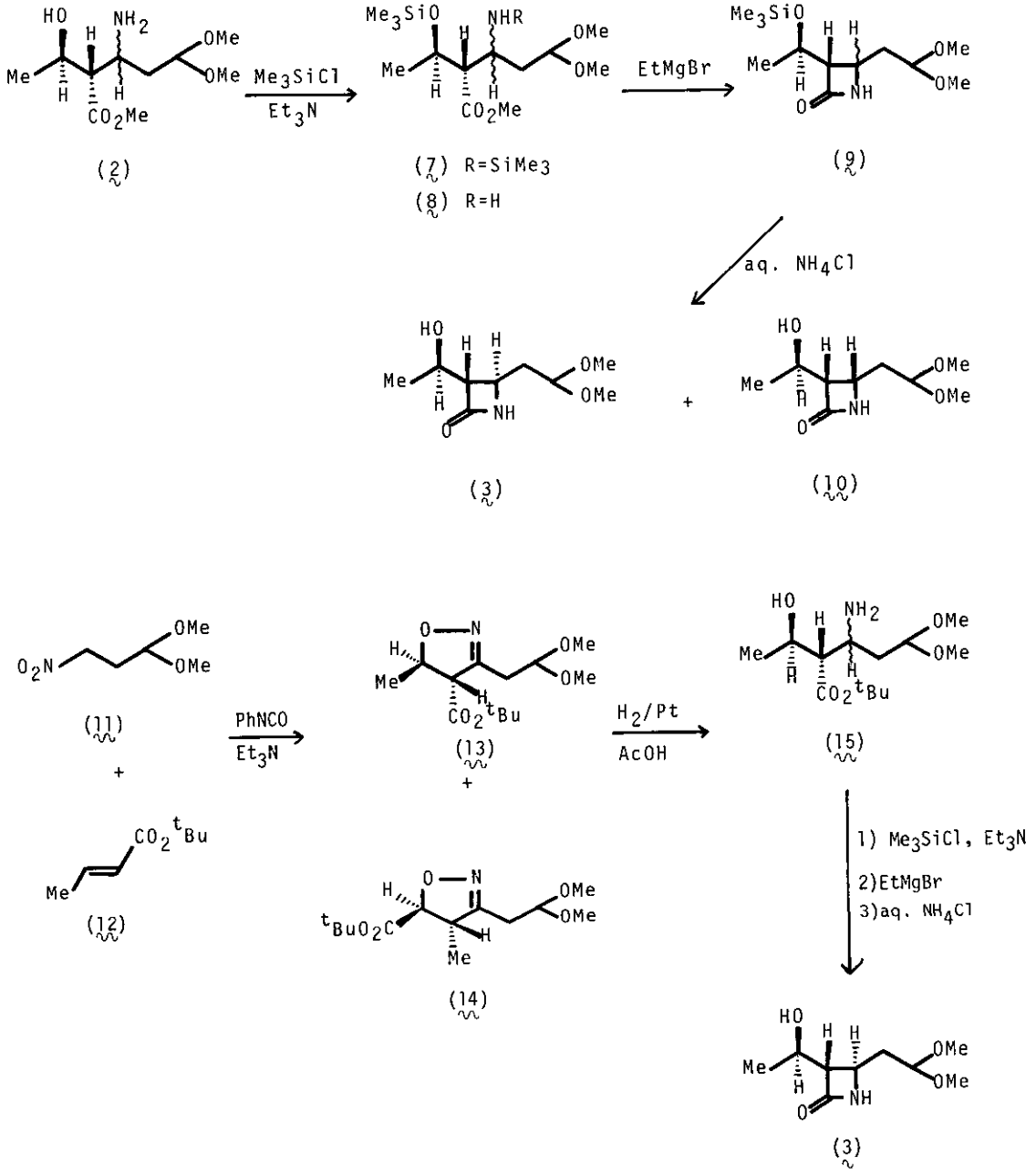
Recently, we reported the formal total synthesis of thienamycin (5) and descysteaminylthienamycin (6) through the isoxazoline derivative (1)[1,2]. Since the main reduction product of 1 was the undesired stereoisomer, the required trans-azetidinone (3), synthesised from the resultant amino ester mixture (2) by lactam formation on the derived amino acid using N,N'-dicyclohexylcarbodiimide, was contaminated with its epimer (4), which was unseparable from 3. On the other hand, treatment of 2 with Grignard reagent selectively produced 3 in about 10 % yield. We therefore looked for a more effective synthesis of 3 and here report the improved results.

Firstly, cyclization of 2 using trialkylaluminium[3] was examined, but the yield of 3 was not improved. Consequently it was decided to determine whether protection of the hydroxyl group in 2 would enable a more efficient conversion to 3. Thus, treatment of 2 with excess trimethylsilyl chloride, in the presence of triethylamine in benzene at room temperature, afforded an N,O-disilylated product (7). When the reaction was carried out for a shorter period, using a limited amount of the reagents, a stable trimethylsilyl ether (8) was obtained. On treatment with excess ethylmagnesium bromide[4] in tetrahydrofuran at room temperature, both



(1) (2) (3) (4) (5) (6)

compounds (7 and 8) were converted into a mixture of trans- and cis-azetidinones (9), m/e 276 ($M^+ + 1$), in 63 ∿ 78.5 % yield. The ir spectrum ($CHCl_3$) of this product showed NH group absorption at 3425 cm^{-1} and carbonyl group absorption at 1758 cm^{-1}. The trimethylsilyl group was observed as a singlet (9H) at 0.1 ppm in the nmr spectrum (CCl_4). Deprotection using aqueous ammonium chloride gave the trans- and cis-β-lactams (3 and 10), which were separated by silica gel column chromatography. By this route the trans-β-lactam (3) was synthesised in 20.6 % yield from the isoxazoline (1), while 10 was produced in 38.2 % yield. It was anticipated that reduction of an isoxazoline bearing a bulkier ester group would lead to a higher proportion of the desired amino ester. tert-Butyl ester (13) was therefore prepared by reaction of the nitro acetal (11) and tert-butyl crotonate (12)[5] in the presence of phenyl isocyanate and triethylamine.[6] Thus 4-tert-butoxycarbonylisoxazoline (13) was obtained in 58 % yield along with the separable isomer (14) in 14 % yield. Catalytic reduction of 13 using 5∿6 atoms of hydrogen and Adams catalyst in acetic acid quantitatively yielded an epimeric mixture of the amino ester (15) in the ratio 1 : 1. Interestingly, this mixture 15 afforded only the trans-azetidinone (3) by the aforementioned sequential reaction procedure; silylation, cyclisation with ethylmagnesium bromide, and



(2)

(7) R=SiMe3
(8) R=H

(9)

(3)

(10)

(11)

+

(12)

(13)

+

(14)

(15)

(3)

deprotection. The undesired isomer in the amino ester (15) reacted with ethylmagnesium bromide to give ether-soluble unidentified products. Purification of the β-lactam (3) was readily achieved by utilizing its high water-solubility. According to this method the thienamycin synthetic intermediate (3)[1,2] was obtained in 41.2 % yield from the isoxazoline (13).

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Received, 27th December, 1979