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SYNTHETIC STUDIES ON VIRGINIAMYCIN M2: A USEFUL MODEL EXPERIMENT FOR CONSTRUCTION OF THE 1,3-OXAZOLE MOIETY

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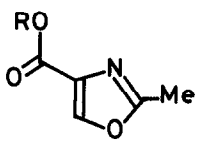
Summary: A useful acylating procedure at the methyl group of 4-*t*-butoxycarbonyl-2-methyl-1,3-oxazole (3) is described. Some curious reactions of 4-*t*-butoxycarbonyl-2-methyl-5-trimethylsilyl-1,3-oxazole (7) are also reported.

Numerous antibiotics of the virginiamycin family (virginiamycin, griseoviridin, mikamycin, *etc.*) have been isolated from *Streptomyces* species.[1] These antibiotics are of interest from a synthetic viewpoint;[2,3,4,5] their molecule consists of a macrocycle which contains lactone and lactam moieties. All of these antibiotics are characteristic of an unusual 1,3-oxazole ring system, a common segment in their molecules,[1] and the synthesis of this 1,3-oxazole moiety is significantly important. Previously, Meyers and Lawson attempted a direct alkylation at the methyl group of 4-carboxy-2-methyl-1,3-oxazole (1) under several basic conditions, but all experiments were not successful.[4] However, they could accomplish the desirable alkylations of 2-methyl group through the open chain precursor of the 1,3-oxazole ring.[4]

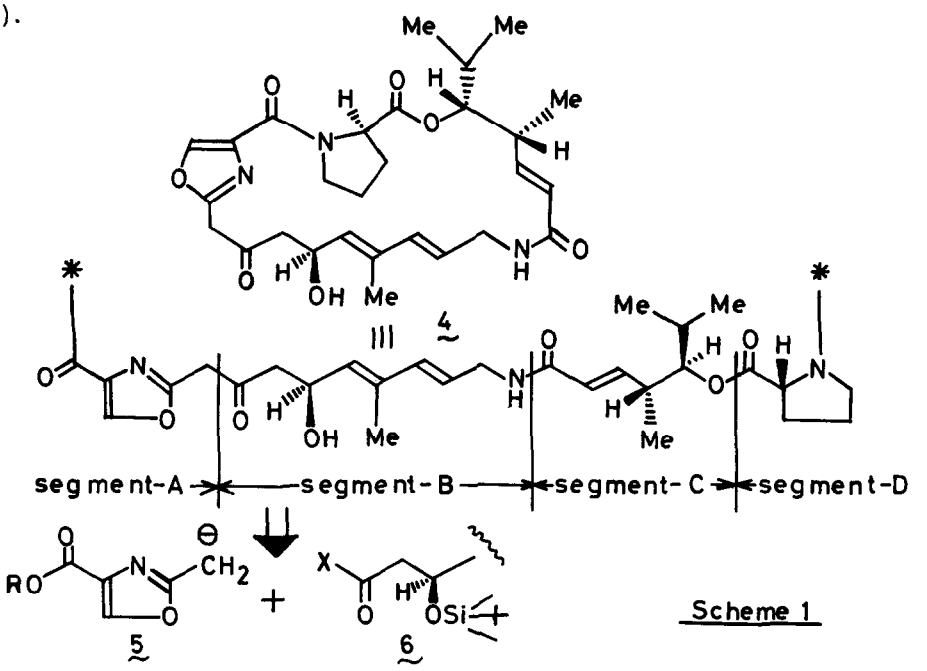


1 R= H 2 R= Et 3 R= t-Bu

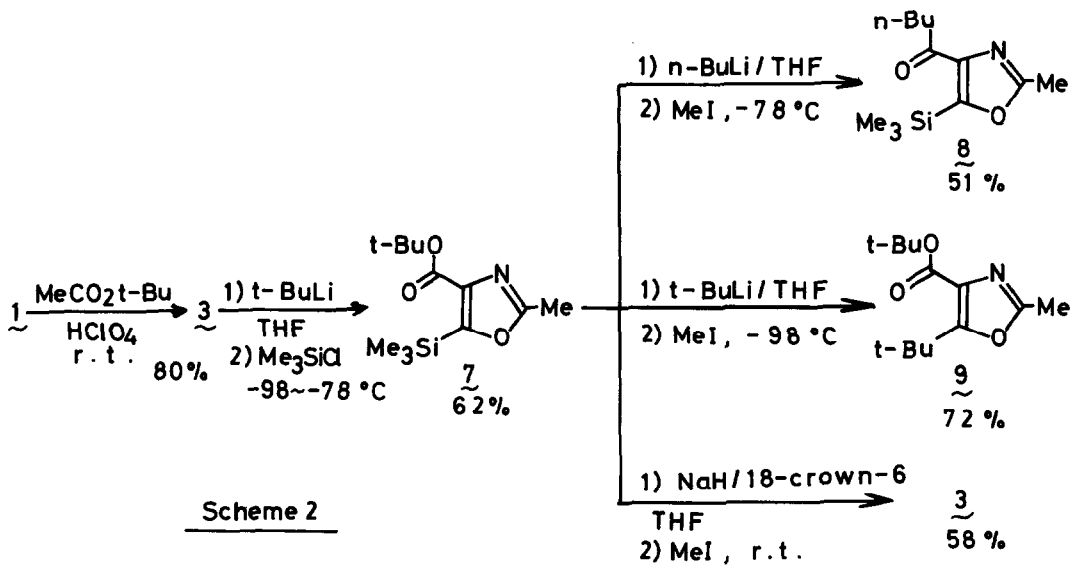
We now wish to report a useful acylating procedure at the methyl group of 4-*t*-butoxycarbonyl-2-methyl-1,3-oxazole (3) and some interesting chemical behavior of compound 7.

As a strategy for the total synthesis of virginiamycin M2 (4), we designed a convergent program involving four segments, A ∿ D, as shown in Scheme 1. In this synthetic program, the connection between segments A and B seemed to be readily accessible by a simple treatment of active carboxylic acid 6, with "anionic" segment-A 5. We first tried acylation of carboxylic acid 1, 4-ethoxycarbonyl-2-methyl-1,3-oxazole (2), and 4-*t*-butoxycarbonyl compound 3 under several metal-containing basic conditions. But, undesirable results were encountered, similarly to the case of Meyers' group[4,6]; the C-5 in 1 and 3 was clarified to be metalated exclusively. Hence, we prepared a C-5 protecting oxazole derivative, 4-*t*-butoxycarbonyl-2-methyl-5-trimethylsilyl-1,3-oxazole (7) in good yield, starting from the Cornforth's carboxylic acid (1)[7] *via* compound 3. On treatment with n-BuLi (1.1 mol equiv.) at -78°C in THF under argon gas and then with MeI (1.1 mol equiv.), 7 gave an unexpected ketone 8 instead of the desirable product methylated at the 2-methyl group.[8] The similar treatment of 7 with *t*-BuLi

(1.1 mol equiv.) at -98°C followed by MeI (1.1 mol equiv.) afforded an unusual Michael-type addition product 9 in good yield under elimination of the trimethylsilyl group. After being stirred with NaH (1.1 mol equiv) in THF with 18-crown-6 (1.1 mol equiv) at room temperature in N_2, 7 was treated with MeI (1.1 mol equiv) to give an unexpected hydrogenolysis product 3 (see Scheme 2).

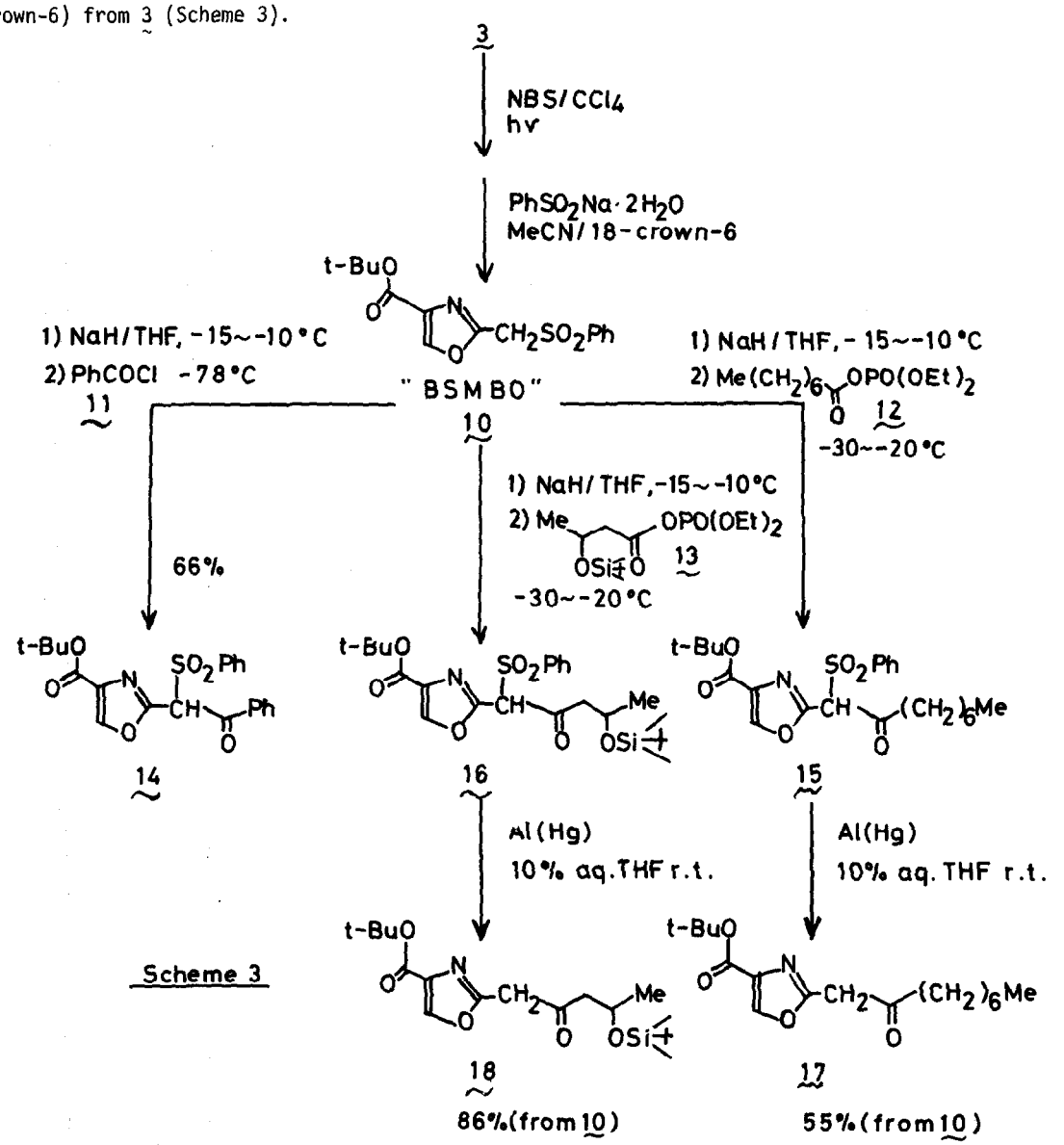


Scheme 1



Scheme 2

These surprizing reactions[9] were overcome by the following modification. Thus, we designed 2-benzenesulfonylmethyl-4-*t*-butoxycarbonyl-1,3-oxazole ("BSMBO") (10) [colorless needles (from EtOH); mp 180 ∿ 182°; IR($CHCl_3$) 1730, 1331, 1160 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.55 (9H, s), 4.61 (2H, s) 7.48 ∿ 7.92 (m, 5H), 8.12 (1H, s)] which was readily available by a chemical conversion[10] (bromination followed by benzenesulfonylation under the presence of catalytic 18-crown-6) from 3 (Scheme 3).

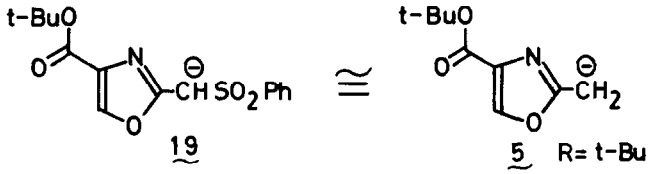


Scheme 3

"BSMBO" (10), dissolved in THF, was added into a solution of NaH (2.2 ∿ 3.3 mol equiv) in THF at -15 ∿ -10°C, and a mixture was stirred for 1 h. Then, an equimolar amount of acylating electrophile 11, 12, or 13 in THF, was dropwise added to the sodio-"BSMBO" solution in THF at

low temperature (11 at -78°C, 12 and 13 at -30°C ∿ -20°C), respectively. After being stirred at the same temperature for 10 h, the usual work-up afforded the corresponding desirable product, 14 [colorless needles (from EtOH); mp 167 ∿ 169°], 15 [colorless needles (from Et_2O-petr. ether); mp 38 ∿ 39°], or 16 [a 1 : 1 ratio of diastereomers (NMR analysis); colorless oil], respectively. Without purification, both compounds 15 and 16 were subjected to the reductive desulfonylation[11] with Al(Hg) in 90% THF-10% water mixture at room temperature to give the desirable product 17 [colorless oil, 55% overall yield from 10; IR($CHCl_3$) 1726 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, J=6 Hz), 1.08 ∿ 1.40 (brS, 10H), 1.58 (s, 9H), 2.51 (t, 2H, J= 7 Hz), 3.93 (s, 2H), 8.11 (s, 1H) ppm; M^+ m/e 309.193] and 18 [colorless needles (from petr. ether), mp 62 ∿ 63°, 86% overall yield from 10; IR($CHCl_3$) 1726 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.05, 0.07 (each 3H, s), 0.87 (s, 9H), 1.18 (3H, d, J=6 Hz), 1.58 (9H, s), 2.40 ∿ 2.85 (2H, m), 3.98 (2H, s), 4.12 ∿ 4.44 (1H, m), 8.11 (1H, s) ppm; M^+ m/e 384], respectively. The excellent yield of 18 can reasonably be attributed to the activation of the carbonyl group in compound 13 due to a favorable neighboring group participation[12] of the t-butyldimethylsilyl group. The synthesis of 18 forms an important model experiment for construction of the 1,3-oxazole moiety of virginiamycin M2 (4).

Thus, we demonstrated that "BSMBO"-carbanion 19 should be effective as a synthon which is equivalent to the anion 5. This approach may make a great contribution to the total synthesis of all virginiamycin-like antibiotics.



19 5

References and Notes

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