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A SIMPLE SOLUTION TO THE OXAZOLE PROBLEM IN VIRGINIAMYCIN M

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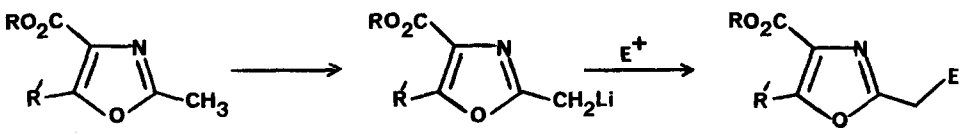
Summary: By first silylating at C5, 2-methyl-1,3-oxazole-4-carboxylic acid may readily be metallated and alkylated at the ring methyl group.

In work related to the total synthesis of griseoviridin and virginiamycin M, two recent Letters[2-3] reported that the unusually acidic proton at C5 of several 2-methyl-4-carboxyoxazoles prevented the formation of anion 5 by direct metallation of the heterocycle. Meyers and Lawson,[2] who were unable to make 5 from 1 or 2, instead alkylated the dianion of methyl α-(α-methoxyethylideneamino)-β-hydroxyacrylate, then cyclized the oxazole precursor to 7 by treatment with BF_3-Et_2O. Fujita *et al.*[3] elected to block the acidic oxazole hydrogen with a trimethylsilyl group, as in 3. However 3 was so susceptible to nucleophilic addition by alkyllithium bases that a sulfonyl substituent was eventually required to activate the ring methyl group.



1 R, R'= H
2 R=alkyl, R'=H
3 R=alkyl, R'=TMS
4 R=H, R'=TMS

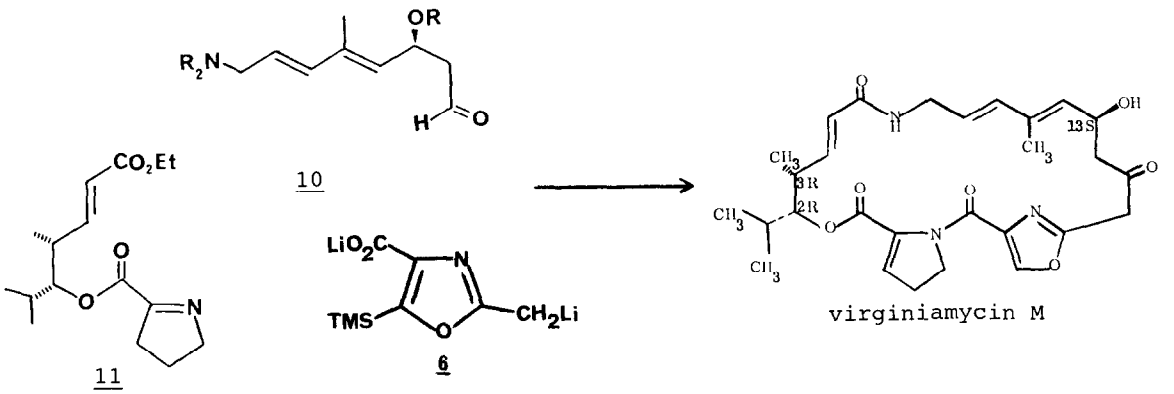
5 R=Li or alkyl
R'=H
6 R=Li, R'=TMS

7 R=H or alkyl
R'=H
8 R=H, R'=TMS
9 R, R'=H

Our own interest[4] in the synthesis of virginiamycin M led us to develop an independent and superior solution to this problem. Here we report that silylacid 4 smoothly formed dianion 6 which reacted with a variety of electrophiles to furnish 2-substituted 1,3-oxazole-4-carboxylic acids 9 after desilylation.

Acid 4 was readily prepared from 1 (2.5 equiv t-BuLi, THF, -40^0; 5 equiv TMSCl; aqueous NH_4Cl workup) in 86% yield. Metallation of 4 with 2 equiv of t-BuLi (THF, -78^0, 2 min) afforded a bright orange solution of dianion 6 that reacted with CH_3OD to afford 8 (E=D), now 77% enriched in deuterium at the C2 methyl. In similar fashion, dianion 6 combined with iodomethane, isobutyraldehyde and acetone to furnish the respective adducts 8, all highly polar substances, in excellent yield: [E=CH_3, 86%, mp $146-7^0$; E=$(CH_3)_2CHCH(OH)$-, 88%, mp $117-18.5^0$; E=$(CH_3)_2C(OH)$-, 90%].[5]

Several desilylation methods were examined, of which the best proved to be treatment with cesium fluoride in methanol. Thus oxazole 8 (E=CH_3) was transformed into 9 (E=CH_3) in quantitative yield (14h, 80^0C).[5] With intermediates 10 and 11 in hand,[6] alkylation of 6 with 10, then acylation of 11 constitutes a highly convergent approach to the virginiamycins.[6-7]



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1. Camille and Henry Dreyfus Teacher Scholar Grant Awardee, 1978-83.

2. A.I. Meyers, J.P. Lawson, Tetrahedron Lett., 22, 3163 (1981).

3. Y. Nagao, S. Yamada, E. Fujita, Tetrahedron Lett., 22, 2291 (1983).

4. R.D. Wood, B. Ganem, Tetrahedron Lett., 23, 707 (1982).

5. Satisfactory IR, NMR and mass spectral data were obtained for these compounds.

6. R.D. Wood, Ph.D. Thesis, Cornell University, 1983.

7. We are indebted to the National Institutes of Health for a predoctoral traineeship to R.D.W. on Grant GM 97273.

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