# Total Synthesis of (−)-Virginiamycin $M_2$ Using Second-Generation Vinylogous Urethane Chemistry

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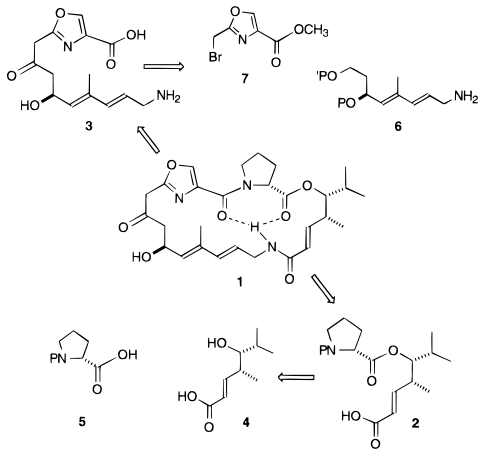
*Received December 28, 1995*

The ever-expanding crisis in antibiotic resistance of bacterial pathogens—the result of either chromosomal changes or the exchange of genetic material *via* plasmids and transposons—is of increasing concern to the medical community.[1] This has prompted increased efforts to find and study new and effective antibiotic species.[2] Total synthesis can play an important role in defining the chemistry of an antibiotic, often leading to its improved efficacy.

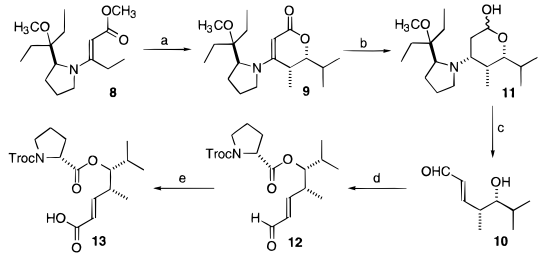
Antibiotics known as the virginiamycins consist of two groups—polyunsaturated macrolactones (type A) and peptidic macrolactones (type B).[3] Mixtures of type A and B virginiamycins exhibit very high potency against a variety of bacteria.[4] Total syntheses of the peptidic virginiamycins (type B) have been reported.[5] However, the synthesis of type A virginiamycins has not been achieved[6]—perhaps due in part to their extreme pH sensitivity.[7] We describe the total synthesis of virginiamycin $M_2$ (**1**), a type A structure of this antibiotic family.[8]

Antibiotic **1** is a 23-membered ring macrolide which possesses one ester and two amide linkages. The compound also contains four stereogenic centers, two of which are proximal to each other. The other two stereogenic centers consist of the amino acid D-proline and an allylic $\beta$-ketoalcohol. Also contained within the 23-membered ring is a 2,4-disubstituted oxazole moiety. Our strategy for the construction of **1** starts with cleavage of the amide and ester linkages of it, which reveals fragments **2** and **3** (Scheme 1). These fragments were further cleaved, as indicated, to afford subunits **4**, **5**, **6**, and **7**. Critical to the assemblage of **1** from these subunits was the nature of the protecting groups carried on them and the timing of their conjoining.

**Scheme 1**



**Scheme 2**[a]



[a] Reagents and conditions: (a) LDA, THF, isobutyraldehyde, −78−0 °C, 87%. (b) Li, $NH_3$, *t*-BuOH, THF, 92%. (c) *m*-CPBA, THF, −78 °C, pyridine, 0 °C, 82%. (d) N-((2,2,2-trichloroethoxy)carbonyl)-D-proline, DCC, DMAP, $CH_2Cl_2$, 92%. (e) $NH_2SO_3H$, $NaClO_2$, THF, $H_2O$, 0 °C, 88%.

We commenced this synthesis with the construction of an analogue of **2** using a new stereoselective aldol lactonization reaction.[9] The lithium enolate of vinylogous urethane **8**, a species which does not contain a $C_2$ symmetric chiral auxiliary, reacts with isobutyraldehyde to afford the vinylogous urethane lactone **9** (87% yield, 96% de)[10] (Scheme 2). Compound **9** was re-formed into the unsaturated aldehyde homoallylic alcohol **10** in two steps by dissolving metal reduction of the former to the amino lactol **11** (92%) followed by oxidative elimination of the amine (82%). The aldehyde alcohol **10** proved only moderately stable and, therefore, was immediately esterified with *N*-((2,2,2-trichloroethoxy)carbonyl)-D-proline (92%). Oxidation of the resulting aldehyde ester **12** under Lindgren's conditions smoothly formed the corresponding acid ester **13** (88%).[11]

Next, we turned our attention to the amine **6**, beginning this construction with the alkylation of the lithium enolate of the vinylogous urethane lactone **14** with isopropyl bromoacetate (Scheme 3). The ester **15**, obtained (93%) as a single stereoisomer from this reaction,[12] was selectively reduced to the corresponding primary alcohol (91%) and then silylated with TBSCl (88%) to afford **16**.

With the single stereogenic center present in **6** established in compound **16**, we submitted the lactonic portion of the latter to

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(3) Virginiamycins are also known as streptogramins, pristinamycins, or synergimycins. For leading reviews of virginiamycin chemistry, see: (a) Di Giambattista, M.; Cocito, C. *J. Antimicrob. Chemother.* **1989**, *24*, 485. (b) Paris, J. M.; Barriere, J. C.; Smith, C.; Bost, P. E. *In Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; pp 183−248. For structure determination of **1**, see: Kingston, D. G. I.; Sarin, P. S.; Todd, L.; Williams, D. H. *J. Chem. Soc. C* **1966**, 1856.
(4) For biological properties of this class of antibiotics, see: (a) Sachiko, G.; Miyazaki, S.; Kaneko, Y. *J. Antimicrob. Chemother.* **1992**, *30* (Suppl. A), 25. (b) Brumfitt, W.; Hamilton-Miller, J. M. T.; Shah, S. *J. Antimicrob. Chemother.* **1992**, *30* (Suppl. A), 29. (c) Corsi, M.; Dal Foeno, G.; Oliosi, B.; Pietra, C.; Van Amsterdam, F. T.; Trist, D. G. *Ann. N.Y. Acad. Sci.* **1994**, *713*, 353. (d) Lam, Y. K. T.; Dai, P.; Zink, D. L.; Smith, A. J.; Lee, N. W.; Freeman, S.; Salvatore, M. J. *J. Antibiot.* **1993**, *46*, 623.
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(7) (a) Rollmann, B.; Rondelet, J. *J. Pharm. Belg.* **1973**, *28*, 425. (b) Rollmann, B.; Rondelet, J. *Pharm. Acta. Helv.* **1972**, *47*, 698.
(8) We warmly congratulate Professor A. I. Meyers and co-workers on the synthesis of madumycin.
(9) A detailed description of this aldol lactonization reaction will be published in the near future.
(10) The absolute stereochemistry of **9** was determined by single-crystal X-ray analysis. For references on other vinylogous urethane enolates to form vinylogous urethane lactones as well as on the chemistry of these lactones, see: (a) Schlessinger, R. H.; Poss, M. A,; Richardson S. *J. Am. Chem. Soc.* **1986**, *108*, 3112. (b) Schlessinger, R. H.; Mjalli, A. M. M.; Adams, A. D.; Springer, J. P. and Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 2992 and references cited therein.
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(12) The stereoselectivity of this reaction was determined by HPLC analysis. For other examples of reactions of this lactone enolate, see ref 10b.

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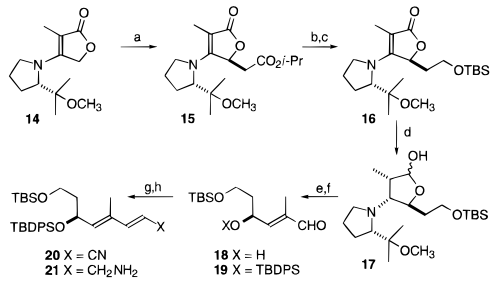
**Scheme 3**[a]




[a] Reagents and conditions: (a) *t*-BuLi, THF, isobutyl bromoacetate, −78−0 °C, 93%. (b) $LiBH_4$, MeOH, THF, 0 °C, 91%. (c) TBSCl, imidazole, $CH_2Cl_2$, 0 °C, 88%. (d) Li, $NH_3$, *t*-BuOH, THF, 86%. (e) *m*-CPBA, 0 °C, pyridine, 0 °C to rt, 75%. (f) TBDPSCl, imidazole, $CH_2Cl_2$, 0 °C, 82%. (g) cyanomethyl diisopropylphosphonate, *t*-BuOK, THF, −78 °C, 87%. (h) $AlH_3$, THF, 0 °C, 78%.

Birch reduction which afforded (86%) the amino lactol **17**. Oxidative elimination of the amine residue from **17** gave (75%) the α,β-unsaturated aldehyde allylic alcohol **18**.

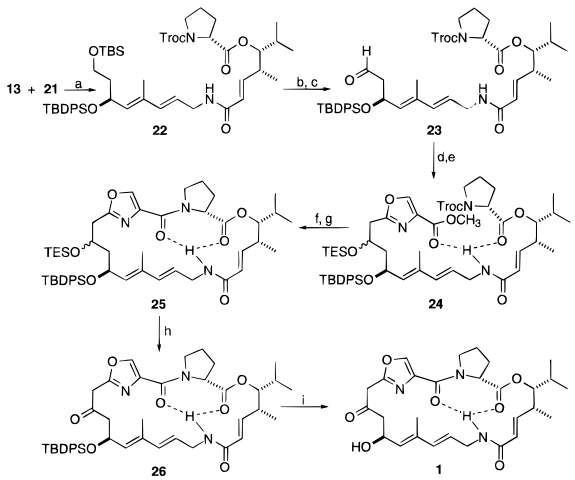
The choice of protecting group for the secondary allylic alcohol present in **18** was critical to this synthesis. It was our plan to complete the synthesis of **1** by removal of this protecting group. Thus, this group had to withstand the gauntlet of reactions necessary to prepare the penultimate synthetic intermediate and yet exhibit sufficient lability to allow its removal under conditions compatible with the limited stability of the natural product.

After tedious experimentation, we settled on the TBDPS group and accordingly prepared (82%) compound **19** from alcohol **18**. Horner−Emmons vinylogation of **19** gave (87%) the (*E*)-nitrile **20**, which on reduction with $AlH_3$ afforded (78%) the allylic amine **21**.[13]

Acid **13** and amine **21** were then combined using Mukaiyama coupling conditions to afford (89%) the corresponding amide **22**[14] (Scheme 4). This amide was then converted (two steps) into its corresponding aldehyde **23** by removal of the TBS protecting group on the primary alcohol (70% HF·pyridine, 82%) followed by oxidation with Dess−Martin periodinane (87%).[15] Compound **23** suffered (67%) Reformatsky addition of **7**[16] onto the aldehyde residue in the presence of Zn dust and $Et_2AlCl$ to give a diastereomeric mixture of secondary alcohols which were immediately silylated (83%) to afford **24**.[17]

The stage was now set for establishing the 23-membered ring of **1**, utilizing the following sequence of reactions. Zinc-mediated removal of the *N*-((2,2,2-trichloroethoxy)carbonyl) group from the proline residue, selective hydrolysis with LiOH of the methyl ester carried by the oxazole ring, and, finally, Mukaiyama amide coupling gave (three steps, 48% overall yield) the desired macrocyclic product **25**.[18]

**Scheme 4**[a]




[a] Reagents and conditions: (a) 2-chloro-1-methylpyridinium iodide, *n*-$Bu_3N$, $CH_2Cl_2$, rt, 89%. (b) 70% HF, pyridine, THF, 0 °C, 82%. (c) Dess−Martin periodinane, $CH_2Cl_2$, rt, 87%. (d) 2.2 equiv of methyl 2-bromomethyl-5-oxazolecarboxylate, 2.4 equiv of Zn dust, 1 equiv of $Et_2AlCl$, rt to 35 °C, 67%. (e) TESOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 83%. (f) 40 equiv of Zn dust, aq $NH_4OAc$, THF, 92%. (g) LiOH, THF/$H_2O$, 9/1, 2-chloro-1-methylpyridinium iodide, *n*-$Bu_3N$, $CH_2Cl_2$, 0.001 N, rt two steps in 52%. (h) THF, AcOH, $H_2O$, (10/4/1). Dess−Martin periodinane, $CH_2Cl_2$, rt, two steps in 61%. (i) 10 equiv of HF·pyridine (1/2), $CH_2Cl_2$, rt, 78%.

At this juncture there remained the problems of re-forming the TES-protected secondary alcohol of **25** into its corresponding ketone **26** and removal of the TBDPS protecting group from this species to unmask the allylic β-hydroxyketone ensemble required by the natural product. Treatment with acetic acid smoothly removed the TES residue, and Dess−Martin periodinane oxidation provided (61% yield over two steps) the penultimate synthetic intermediate **26**.[19] Lastly, reaction of **26** with HF·pyridine (1/2) smoothly desilylated (78%) **26** to give synthetic virginiamycin $M_2$ (**1**), which proved identical in all respects to an authentic sample of the natural product.

**Acknowledgment.** This work is dedicated to Professor Marshall D. Gates on the occasion of his 80th birthday. Financial support of this work by Grant CA-28544 (NIH), by Sherman Clarke fellowship (to Y.-J. L.), and by Merck Sharp and Dohme fellowship (to Y.-J. L.) is gratefully acknowledged. We thank Professor D. G. I. Kingston for providing an authentic virginiamycin $M_2$ sample, and Dr. J. M. Paris (Rhone-Poulenc Rorer, France) for providing 2H Virginiamycin $M_2$ spectra. We thank Thomas R. R. Pettus for invaluable help in preparing this manuscript. Early contributors to this problem include Dr. Vinod Patel, Dr. Derek Von Langen, Dr. Edwin Iwanowicz, and Dr. Peter Lin.

**Supporting Information Available:** Experimental procedures for **1**, **9**−**13**, and **15**−**26**; $^1$H COSY spectra of natural and synthetic **1** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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