Published in final edited form as:
Org Lett. 2007 August 2; 9(16): 3105–3108. doi:10.1021/ol071145e.

De Novo Formal Synthesis of (—)-Virginiamycin M_2 via the Asymmetric Hydration of Dienoates

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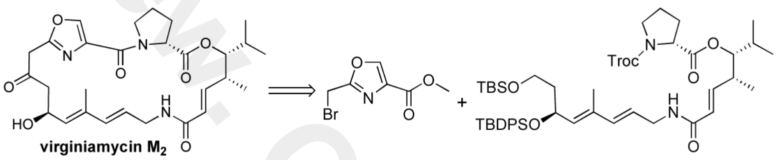
Abstract



A de novo approach to the formal total synthesis of the macrolide natural product (—)-virginiamycin M_2 has been achieved via a convergent approach. The absolute and relative stereochemistry of the non-peptide portion of (—)-virginiamycin M_2 was introduced by two Sharpless asymmetric dihydroxylation reactions.

The problem associated with new microbes that develop resistance mechanisms to antibiotics has fueled the never-ending search for new antibacterial agents.[1] In fact, infections from methicillin-resistant *S. aureus* (MRSA) organism have become increasingly common.[2] More alarming is the discovery of vancomycin resistant *S. aureas* organisms.[3] Currently three antibiotics (linezolid, daptomycin, and quinupristin-dalfopristin) have been approved to combat these infections. The oldest of the three quinupristin-dalfopristin is the admixture of two types of streptogramin antibiotics, dalfopristin (type A) and quinupristin (type B) (Figure 1), which derives its potency by the synergistic binding of two weak ribosome binders.[1]

The type A component dalfopristin is a semi-synthetic compound prepared by a sulfinic acid addition across the dehydro-proline portion of virginiamycin M_1 (Figure 2), which enhances activity by providing improved solubility.[1c] As part of a program aimed at developing new antibiotic structures we became interested in the synthesis of both virginiamycin M_2 as well as the synthesis of a library of novel virginiamycin analogues. We envisioned replacing the sulfone group on the proline with an aminoglycoside sugar, with the hope of discovering new synergistic binding.[4] As a prelude to this medicinal chemistry studies/library synthesis, we decided to investigate the feasibility by conducting a formal total synthesis.

In addition to its potent antibiotic activity, the structural novelty of virginiamycin M_2 has also attracted the attention of the synthetic community.[5,6] To date several total syntheses of the type A streptogramin antibiotics have been completed,[5] along with a formal total synthesis.[6] While all of the previous syntheses of the streptogramin class of antibiotics derived their asymmetry from the chiral pool, enzymatic resolution and/or chiral auxilaries,[5] we were interested in a de novo asymmetric approach that would use asymmetric catalysis to install the stereocenters of the nonaminoacid portion of type A streptogramins. Herein we describe our

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

successful efforts to implement this strategy for the de novo formal total synthesis of virginiamycin M_2.

Retrosynthetically, virginiamycin M_2 (**1**) has been derived from the seco-macrolide **2**,[5b] which in turn could be prepared from the known oxazole **3**, and triene **4**. Previously, Schlessinger had demonstrated the conversion of **4** and **3** to Virginiamycin M_2 (**1**).[5a] In our strategy (Scheme 1), we envisioned the triene **4** as being assembled from D-proline, allylic amine **5** and δ-hydroxy ester **6**. Finally we planed to install the asymmetry of these two fragments by the application of a regioselective Sharpless asymmetric dihydroxylation of diene fragments **7** and **8**.[7,8] In particular, we were interested in using our asymmetric hydration strategy for the preparation of the syn-γ-substituted δ-hydroxyenoate **6**.[9]

To access useful quantities of dienoate **8**, an efficient 5-step approach was developed (Scheme 2). While the route featured standard Wittig/Horner Emmons olefination chemistry, key to practical nature of this approach was the recognition that TFA can catalyze the stereoselective isomerization of enal **11** to the more stable *E*-isomer (98:2), which when treated with the stablized Wittig reagent provided good yields of **8** (72%).[10] While we previously had demonstrated the asymmetric hydration of **8** to the enantiomer of **6**, because of the pseudo-enantiomeric nature of the Sharpless reagents (DHQ/DHQD) the regiochemistry of this reaction was an open question. In practice, we found that the monomeric 4-methyl-2-quinolylether linked DHQD ligand provided the best balance in terms of regio- and stereochemistry.[11] Thus when **8** was dihydroxylated with the OsO_4/DHQD-4-MEQ reagent good yields of diol **12** as a single regioisomer was isolated (75%, 90% ee), which was cyclized into carbonate**13** in good overall yield (90%). Exposure of carbonate **13** to the palladium(0) catalyzed reduction conditions (HCO_2H/Et_3N) provided δ-hydroxy enoate **6** in good yield (98%).

With δ-hydroxyenoate **6** in hand, we next investigated the synthesis of amine **5** (Scheme 3). Unfortunately, our initial plan to use a regioselective asymmetric dihydroxylation of dienoate **7**, was thwarted by our inability to prepare **7** by Horner-Emmons olefination of **15**. Instead of **7** only Michael addition products were observed. Thus, we decided to preform the dihydroxylation a step earlier on enone **15**, which could be easily prepared in three steps (63%) from 1,3-propane diol (**14**). Exposure of enone **15** to the typical Sharpless asymmetric dihydroxylation procedures gave a good yield (71%) of diol **16** and in high enantiopurity (90% ee). The diol product was protected as an acetonide (2,2-DMP/5% CSA, 72%) and the ketone product **17** underwent Horner-Emmons olefination to form enoate **18** (84%; 10:1, *E/Z*). The enoate **18** was reduced with DibalH to give allylic alcohol **19**, which in turn was converted into allylic nitrile **20** by a 2-step protocol (PPh_3/I_2 then NaCN in AN; 50%). Base promoted elimination (K_2CO_3/MeOH, 81%) of **20** stereoselectively gave the *E*,*E*-diene **21** (98:2, *EE:EZ*). The secondary allylic alcohol in **21** was protected as a TBDPS-ether (TBDPSCl/imid, 89%) and the nitrile was cleanly reduced with AlH_3 to give amine **5** in good yield (70%).[12]

We next investigated the synthesis of the first fragment coupling product ester **25** (Scheme 4). While **24** could be prepared in one step from a Troc-protected D-proline, for this model system, we decided to use the already available Boc-protected D-proline **22**. Coupling proline **22** and alcohol **6** with DCC/DMAP followed by deprotection of the Boc-group (TFA) gave good yields of amine **23** (88%, 2 steps). The secondary amine **23** was protected with TrocCl/Pyr (71%) to give ester **24**, which was selectively hydrolyzed (NaOH, 56%) to give the desired carboxylic acid **25**.[13]

With the final two fragments **5** and **25** in hand, we investigated their coupling to form our desired target molecule **4** (Scheme 5). After screening several coupling procedures we found the DCC/DMAP to give the best yields and to be operationally the simplest. Thus, exposing a

1:1 mixture of **5** and **25** to a CH_2Cl_2 solution of DCC/DMAP gave 82% yield of amide **4**, which was physically (optical rotation) and spectroscopically (^1H NMR, ^{13}C NMR, IR and MS) identical to the material previously reported by Schlessinger.[14]

In conclusion, a short formal de novo asymmetric synthesis of virginiamycin M_2 has been developed. This highly enantio- and diastereocontrolled route illustrates the utility of our dienoate asymmetric hydration strategy for natural product synthesis. Further application of this approach to the synthesis of mixed aminoglycoside/virginiamycin M_2 analogues is ongoing and these results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the NIH (GM63150) and NSF (CHE-0415469) for the support of our research program and NSF-EPSCoR (0314742) for a 600 MHz NMR and an LTQ-FT Mass Spectrometer at WVU.

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11. In addition to the electronic effect, we have found subtle steric effects can lead to the formation of regioisomers in the Sharpless asymmetric dihydroxylation reaction of dienoates, see refs 7 and 9a.

12. The chemoselective AlH_3 reduction of dienylnitriles like **21** is precedented, see ref. 5a.

13. We surmised that this lower than expected yield was due to the water solubility of **25**, no elimination to dienoate **8** was observed.

14. Unfortunately a typographical error occurs in the data reported by Schlessinger such that the 11 signals below 24 ppm are missing from their reported ^{13}C NMR spectral data. The remaining 25 signals above 24 ppm did match the reported data, see ref. 5a.

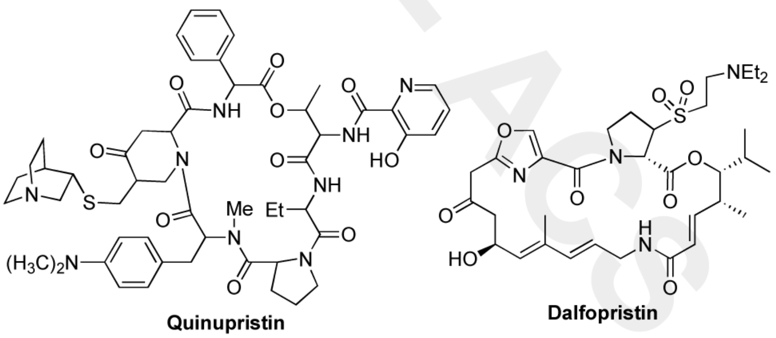


Figure 1.
Quinupristin-dalfopristin

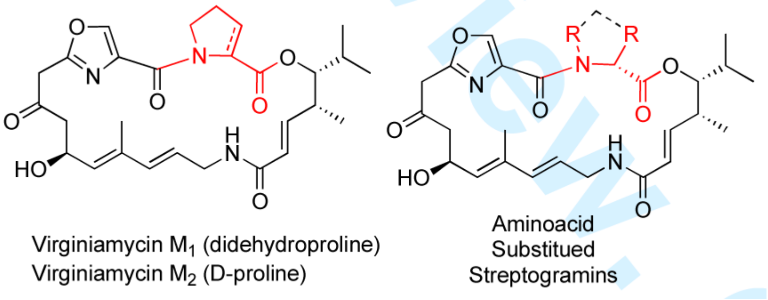
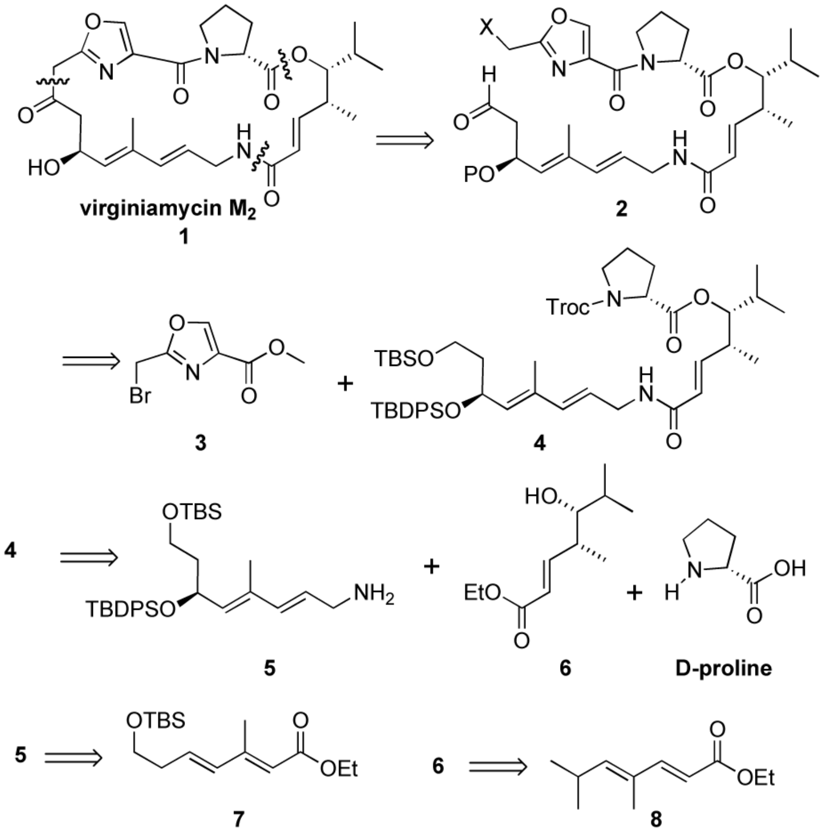
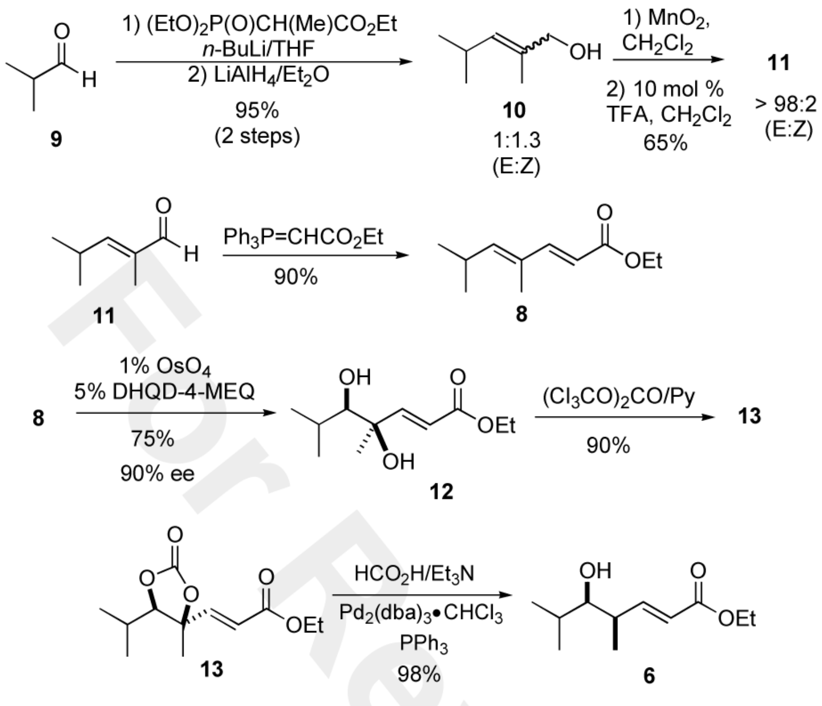


Figure 2.

Type A Streptogramins

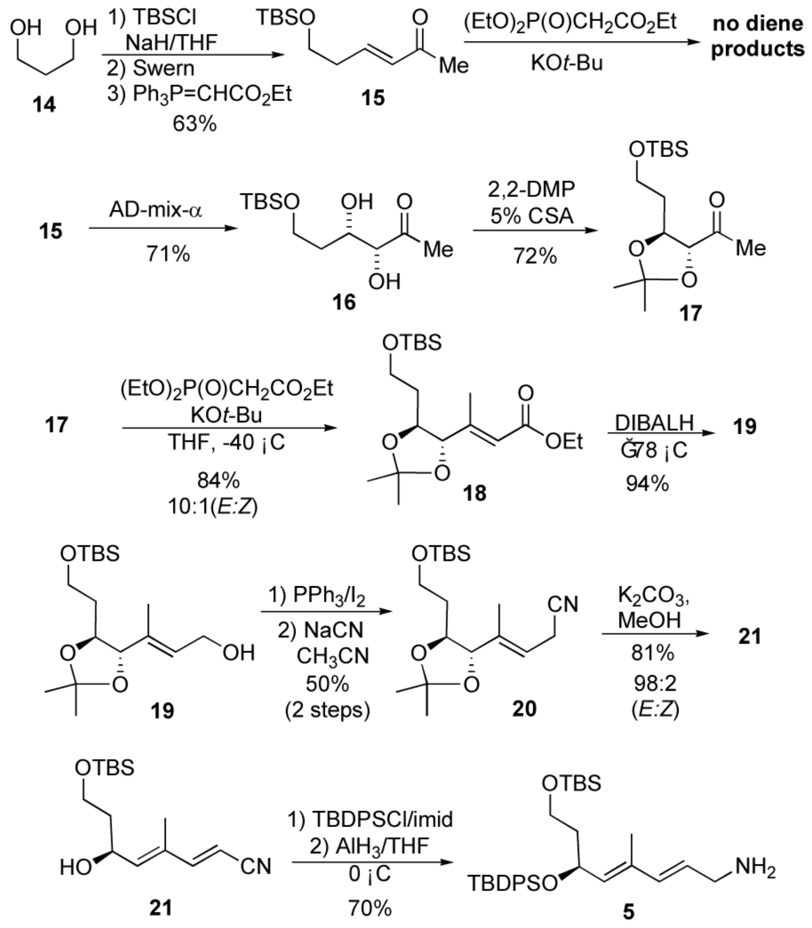


Scheme 1.
Retrosynthesis of (—)-Virginiamycin M$_2$ (**1**)



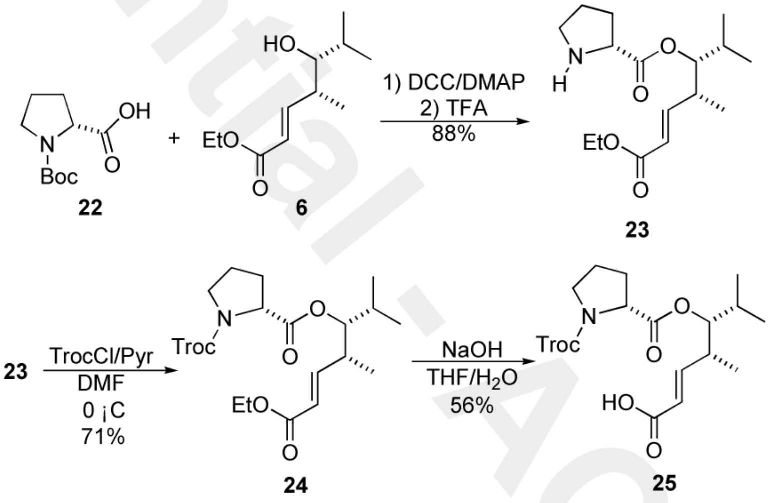
Scheme 2.

Asymmetric hydration of dienoate**8**



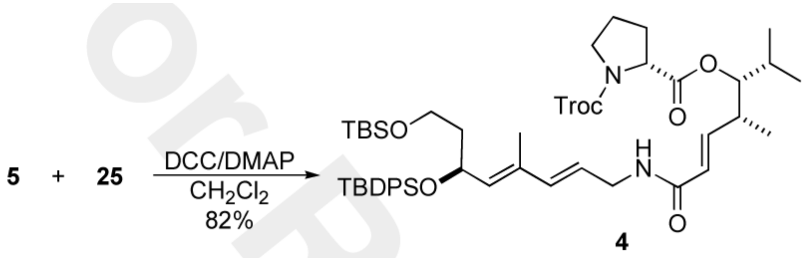
Scheme 3.

De novo synthesis of allylic amine **5**



Scheme 4.

Synthesis of proline ester **25**



Scheme 5.

Completion of the formal synthesis of (—)-virginiamycin M$_2$