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

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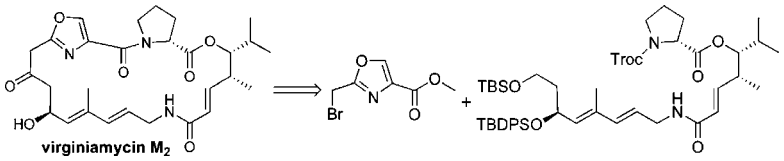
ABSTRACT



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 nonpeptide 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. aureus* 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 dehydroproline 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 these 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

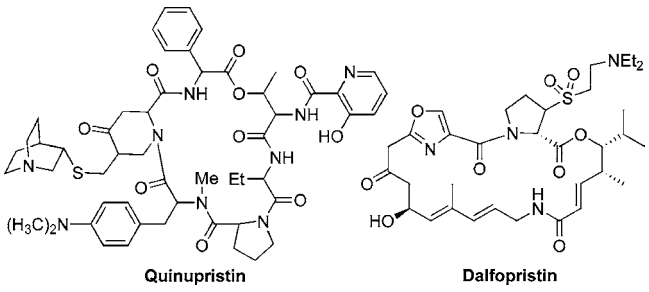


Figure 1. Quinupristin-dalfopristin.

(1) (a) Walsh, C. T. *Nature* **2000**, *406*, 775−781. (b) Chang, S.; Sievert, D. M.; Hageman, J. C.; Boulton, M. L.; Tenover, F. C.; Downes, F. P.; Shah, S.; Rudrik, J. T.; Pupp, G. R.; Brown, W. J.; Cardo, D.; Fridkin, S. K. *New Engl. J. Med.* **2003**, *348*, 1342−1349 and refs therein. (c) Manthous, C. A.; Amaoteng-Adjepong, Y. *Chest* **2000**, *118*, 9−11. For clinical and pharmacological background on streptomycin antibiotics, see: (d) Barriere, J. C.; Berthaud, N.; Beyer, D.; Dutka-Malen, S.; Paris, J. M.; Desnottes, J. F. *Curr. Pharm. Des.* **1998**, *4*, 155−180. (e) Manzella, J. P. *Am. Fam. Physician* **2001**, *64*, 1863−1866. (f) Mukhtar, T. A.; Wright, G. D. *Chem. Rev.* **2005**, *105*, 529−542. (g) Porse, B. T.; Garrett, R. A. *J. Mol. Biol.* **1999**, *286*, 375. For synthesis of new quinolone class antibiotic active against VRSA, see: (h) de Souza, N. J.; Gupte, S. V.; Deshpande, P. K.; Desai, V. N.; Bhawsar, S. B.; Yeole, R. D.; Shukla, M. C.; Strahilevitz, J.; Hooper, D. C.; Bozdogan, B.; Applebaum, P. C.; Jacobs, M. R.; Shetty, N.; Patel, M. V.; Jha, R.; Khorakiwala, H. F. *J. Med. Chem.* **2005**, *48*, 5232−5242.
(2) McCaughey, B. *N.Y. Times* Nov 14, 2006, p 27.
(3) Schito, G. C. *Clin. Microbiol. Infect.* **2006**, *12*, 3−8.

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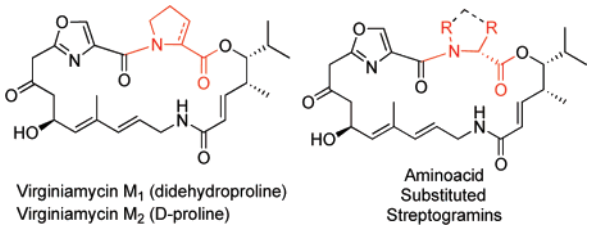
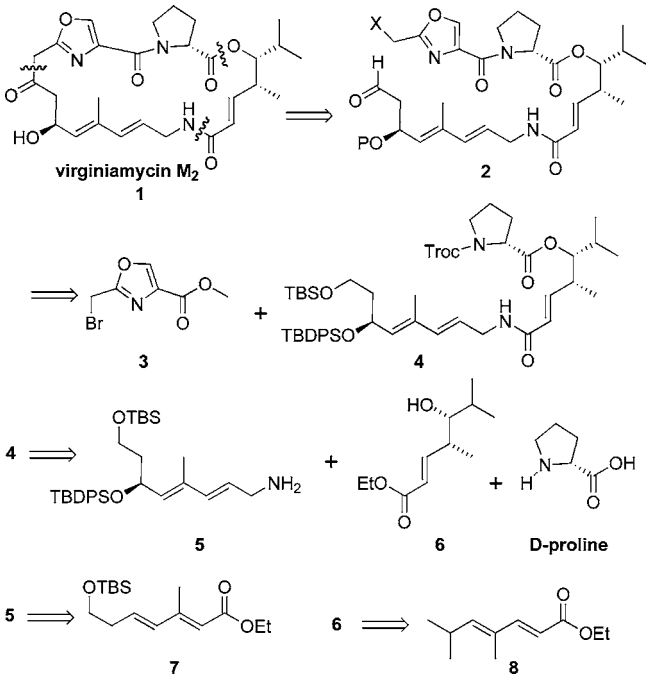


Figure 2. Type A streptogramins.

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 auxiliaries,[5] we were interested in a de novo asymmetric approach that would use asymmetric catalysis to install the stereocenters of the non-amino acid portion of type A streptogramins. Herein we describe our successful efforts to implement this strategy for the de novo formal total synthesis of virginiamycin M_2.

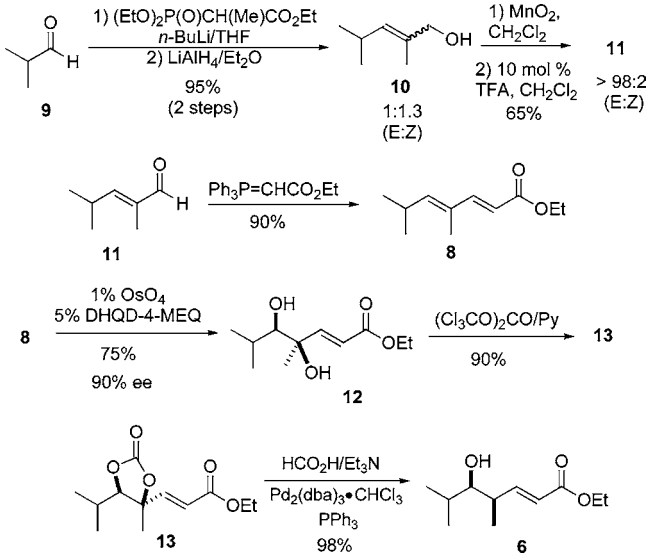
Retrosynthetically, virginiamycin M_2 (**1**) has been derived from the seco-macrolide **2**,[5b] which in turn could be prepared from the known oxazole **3**, and triene **4**. Previously, Schlessinger had demonstrated the conversion of **4** and **3** to virginiamycin M_2 (**1**).[5a] In our strategy (Scheme 1), we envisioned the triene **4** as being assembled from D-proline, allylic amine **5**, and δ-hydroxy ester **6**. Finally, we planned 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]

Scheme 1. Retrosynthesis of (−)-Virginiamycin M_2 (**1**)



To access useful quantities of dienoate **8**, an efficient five-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 stabilized 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

Scheme 2. Asymmetric Hydration of Dienoate **8**



(4) For conformational studies of the virginiamycin type antibiotics, see: (a) Dang, J.; Metzger, R. P.; Brownlee, R. T. C.; Chai, A. N.; Separovic, F. *Eur. J. Biophys.* **2005**, *34*, 383−388. (b) Dang, J.; Separovic, F.; Brownlee, R. T. C.; Metzger, R. P. *J. Org. Biomol. Chem.* **2004**, *2*, 2919−2924. (c) Dang, J.; Separovic, F.; Brownlee, R. T. C.; Metzger, R. P. *Aust. J. Chem.* **2004**, *57*, 415−418.

(5) For the first total synthesis of virginiamycin M_2, see: (a) Schlessinger, R. H.; Li, Y.-J. *J. Am. Chem. Soc.* **1996**, *118*, 3301−3302. For the second, see: (b) Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 3149−3152. For the first total synthesis of madumycin II, see: (c) Tavares, F.; Lawson, J. P.; Meyers A. I. *J. Am. Chem. Soc.* **1996**, *118*, 3303−3304. For the second, see: (d) Ghosh, A. K.; Liu, W. *J. Org. Chem.* **1997**, *62*, 7908−7909.

(6) Brennan, C. J.; Campagne, J.-M. *Tetrahedron Lett.* **2001**, *42*, 5195−5197.

(7) The regioselectivity of the asymmetric dihydroxylation of di- and trienoates has been studied by Sharpless. See: (a) Berker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345−1376. Our group: (b) Zhang, Y.; O'Doherty, G. A. *Tetrahedron* **2005**, *61*, 6337−6351.

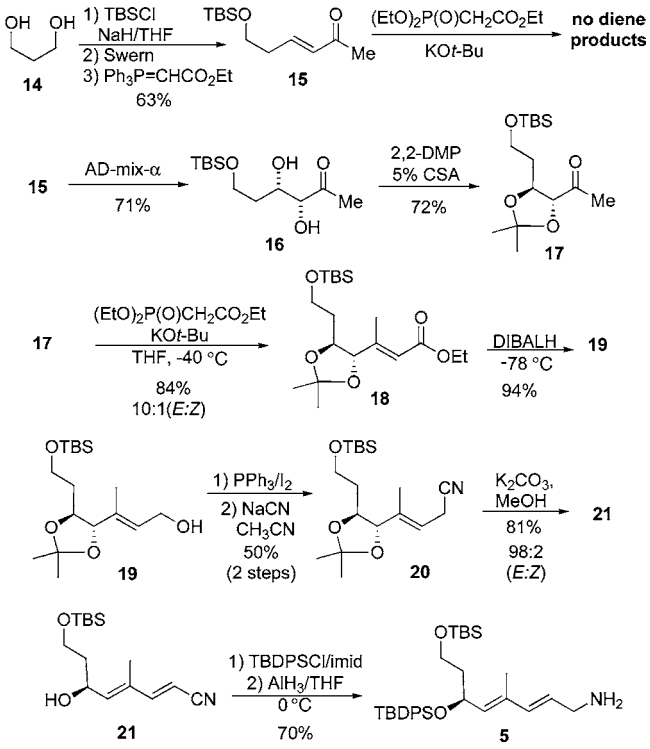
(8) For the use of this approach in synthesis, see: (a) Smith, A. B.; Walsh, S. P.; Frohn, M.; Duffey, M. O. *Org. Lett.* **2005**, *7*, 139−142. (b) Ahmed, Md. M.; Akhmedov, N.; Cui, H.; Friedrich, D.; O'Doherty, G. A. *Heterocycles* **2006**, *70*, 223−233. (c) Ahmed, Md. M.; Cui, H.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 6686−6689. (d) Gao, D.; O'Doherty, G. A. *J. Org. Chem.* **2005**, *70*, 9932−9939. (e) Ahmed, Md. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2005**, *46*, 4151−4155.

(9) (a) Ahmed, Md.; Mortensen, M. M. S.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 7741−7746. (b) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049−1052. For its use in the synthesis of natural products, see: (c) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 3987−3990. (d) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087−6090.

(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 were 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-hydroxyenoate **6** in good yield (98%).

With δ-hydroxyenoate **6** in hand, we next investigated the synthesis of amine **5** (Scheme 3). Unfortunately, our initial

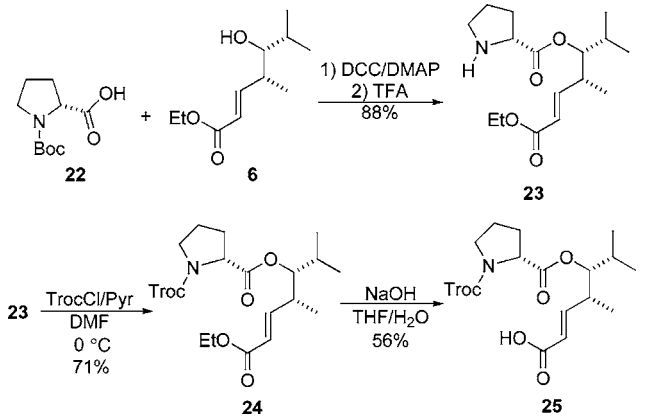
Scheme 3. De Novo Synthesis of Allylic Amine **5**



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 two-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

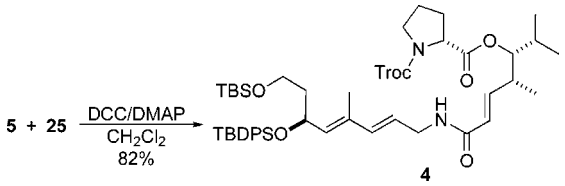
Scheme 4. Synthesis of Proline Ester **25**



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%, two 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

Scheme 5. Completion of the Formal Synthesis of (−)-Virginiamycin M_2



procedures, we found the DCC/DMAP to give the best yields and to be operationally the simplest. Thus, exposing a 1:1

(10) We have found this acid-catalyzed isomerization of α,β-unsaturated aldehydes to be quite general and very useful in our diene syntheses. See: Varelis, P.; Johnson, B. *Aust. J. Chem.* **1997**, *50*, 43−52.

(11) In addition to the electronic effect, we have found that 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.

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 (^{1}H 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.

(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.

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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.

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