Title
Modular Synthesis of Streptogramin Antibiotics

Journal
Synlett, 32(07)

ISSN
0936-5214

Authors
Li, Qi
Seiple, Ian B

Publication Date
2021-04-01

DOI
10.1055/a-1293-9655

Peer reviewed

HHS Public Access
Author manuscript
Synlett. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:
Synlett. 2021 April ; 32(7): 647–654. doi:10.1055/a-1293-9655.

Modular synthesis of streptogramin antibiotics

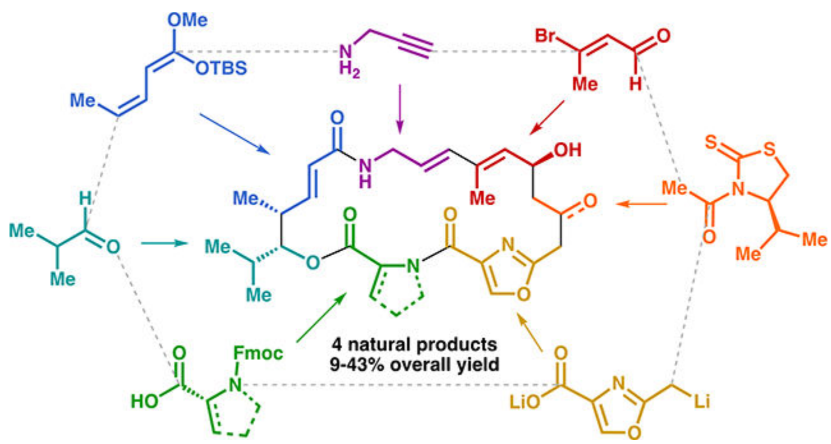
Qi Li[*,a], **Ian B. Seiple**[a]

[a]Department of Pharmaceutical Chemistry and Cardiovascular Research Institute, University of California, San Francisco, San Francisco, California 94158, United States

Abstract

Streptogramins are antibiotics produced by several species of *Streptomyces* bacteria that are used in both human and veterinary medicine. Group A streptogramins comprise 23-membered macrocyclic polyketide/nonribosomal peptide hybrids for which several innovative, fully synthetic routes have been developed. Herein we describe in detail our scalable routes to natural group A streptogramins and compare these routes to other reported syntheses.

Graphical Abstract



Keywords

antibiotics; natural products; virginiamycin; pristinamycin; modular synthesis; infectious disease

1. Introduction

Public health has been seriously threatened by antimicrobial resistance (AMR). Reports from the Centers for Disease Control and Prevention have estimated annual deaths from AMR infections in the United States to be 23,000–35,000,[1a] although a recent report estimated that the number may be closer to 150,000.[1b] Natural product antibiotics are useful both as drugs and as starting materials for further optimization, but co-evolution of resistance mechanisms shorten the clinical lifetime of any given class.[2] Semisynthesis, or

[*]indicates the main/corresponding author. qi.li2@ucsf.edu.

chemical modification of natural products that are obtained through fermentation, serves as a powerful tool to improve classes of natural antimicrobials semisynthesis is inherently limited to chemistry that is compatible with an intact natural product scaffold.[3] Fully synthetic strategies can overcome this limitation, but are challenging to develop for the complex molecular scaffolds of many classes of antibiotics.[3]

Streptogramin antibiotics (also known as virginiamycins, madumycins, and pristinamycins, Figure 1A), which were produced by several species of *Streptomyces*, comprise two structurally distinct subgroups: group A (23-membered macrocyclic polyketide/nonribosomal peptide hybrids) and group B (19-membered macrocyclic depsipeptides).[4] Each subgroup exhibits inhibitory activities against Gram-positive bacteria, and the combination of the two groups often results in syngergistic and bactericidal activity.[5] The first clinically used streptogramins antibiotic in the United States (trade marked as Synercid), a 70:30 combination of dalfopristin (**9**, group A) and quinupristin (**10**, group B), which are derived semi-synthetically from virginiamycin M1 (**1**) and pristinamycin IA (**8**), was approved by FDA for the treatment of severe bacterial infections caused by vancomycin-resistant *Enterococcus faecium* in 1999.[6] In the two decades following, NXL-103, an oral combination of semi-synthetic streptogramins flopristin (**11**) and linopristin (**12**), underwent a successful phase-II clinical trial, but no further development has been reported in 2010.[7] Importantly, none of these semisynthetic streptogramins overcame major resistance mechanisms to the class such as Cfr resistance[8,9] or Vat resistance.[10]

Our laboratory is interested in developing fully synthetic routes to group A streptogramin antibiotics to enable exploration of structure–function relationships, improvement of activity, and avoidance of resistance mechanisms. Herein, we describe in detail the development of two routes to natural group A streptogramin antibiotics from simple chemical building blocks. Our initial route features a Stille macrocyclization reaction and provides access to four natural products in up to 38% yield over 6–8 steps.[11a] Our second-generation route avoids alkyl tin species by harnessing ring-closing metathesis to close the macrocycle. This route provided virginiamycin M2 (**2**) in 6 steps and up to 43% overall yield.[11b] We have applied these routes to the synthesis of novel group A streptogramins that overcome resistance mechanisms in several species of Gram-positive bacteria.[11c]

Several elegant chemical syntheses of group A streptogramins have appeared in the literature. In 1996, Schlessinger and colleagues published the first total synthesis of virginiamycin M2 (**2**), featuring construction of the *syn*-gamma-hydroxyl-(*E*)-unsaturated ester and the trisubstituted-diene by vinylogous urethane chemistry and formation of the 23-membered ring via macrolactamization.[12] This report emerged concomitantly with the first total synthesis of madumycin II (**4**) by the Meyers group in 29 steps with an overall yield of 1.8% from malic acid. The Meyers group also disclosed the first total synthesis of griseoviridin (**6**) in 2000, which featured a ring-closing metathesis to form the macrocycle.[13] Panek reported an elegant route to virginiamycin M2 (**1**) in 6% overall yield in 10 linear steps by means of alkyne–alkyne reductive cross coupling.[14] Other syntheses of these and related streptogramins have also emerged.[15] To the best of our knowledge, fully synthetic routes to madumycin I (**3**) and virginiamycin M1 (**1**) had not been disclosed until we published in 2017.[11a]

2. Modular, scalable synthesis of group A streptogramins

We initially sought to develop a short, scalable route to natural group A streptogramins. Our retrosynthetic analysis of virginiamycin M1 (**1**) is depicted in scheme 1A. We envisioned access to **1** from two halves of approximately equal complexity (**13** and **14**) by means of amidation and Stille coupling. The choice of a Stille reaction enabled the use of a stable vinylstannane which is compatible with the chemistry of the route, including the coupling of the two halves. Left half imine **13** could be synthesized from propargyl amine (**15**), Fmoc-D-proline (**16**), and δ-hydroxy-enoate **17** by means of esterification, amidation, hydrostannylation, and amine to imine oxidation. Vinyligous Mukaiyama aldol reaction between **18** and **19** would provide **17**. The right half **14** could be accessed by displacement of an auxiliary in an intermediate such as **21** using oxazole dianion **20**. β-Silyloxy carboxylate **21** is a retron for a directed aldol reaction between building blocks **22** and **23**.

Our synthesis of left half **13** commenced with Mukaiyama vinylogous aldol reaction of dienol ether **18** with isobutylaldehyde (**19**) using chiral oxazaborolidine (**24**) as a catalyst providing enoate **17** in 94% yield and 87% ee.[16] Amidation of **17** with propargylamine (**15**) in the presence of trimethylaluminum, followed by hydrostannylation of the resulting terminal alkyne mediated by copper produced **25** in 90% yield over 2 steps. Importantly, the secondary alcohol was left unmasked during these steps, which saves at least two steps in the synthesis of the half. All attempts to directly introduce dehydroproline were unsuccessful, necessitating a two-step sequence to reach the desired state of saturation in the proline ring to match virginiamycin M1 (**1**). Thus, D-proline was introduced as its Fmoc-carbamate form **16** using DCC in the presence of catalytic amount of DMAP, followed by the addition of diethylamine to cleave the Fmoc group in a single operation. Subsequent selective oxidation of the amine in the presence of iodosylbenzene[17] produced left half **13** in 81% yield over 2 steps. Overall, left half **13** can be prepared from building blocks **16**, **18** and **19** in 5 steps in 68% overall yield on multigram-scale.

Our synthesis of right half **14** commenced with the Crimmins aldol coupling of (*E*)-3-bromobut-2-enal (**22**, available in 3 steps from crotyl alcohol) and chiral acetyl thiazolidinethione **23** in presence of $TiCl_4$ and $^{i}Pr_2EtN$, providing compound **26** in 64% yield as a single diastereomer.[18] The resulting hydroxyl group was protected by with TBSOTf, delivering *β*- silyloxyimide **27** in 92% yield. The resulting β-silyloxyimide **27** was exposed to the dianion of oxazole **28**, which contains a trimethylsilyl function at C3 to prevent deprotonation of the oxazole ring,[19] furnishing the right half acid **14** directly and efficiently in 71% yield. The route to the right half **14** proceeds in 42% overall yield from **22**, **23** and **28** and has enabled the preparation of over 10 grams of **14**.

The coupling of the two halves proved to be quite challenging, likely due to the low nucleophilicity of the 2,3-dehydroproline function. We found that commonly used amide bond-forming reagents (e.g., HATU, T_3P, Mukauyama reagent, BOP-Cl) were ineffective at coupling **13** to right half **14**. Successful coupling was finally achieved by initial conversion of **14** to an acid chloride with Ghosez's reagent,[20] followed by exposure to a solution of imine **13** and 2,6-lutidine in dichloromethane, which reliably provided macrocycle precursor **29** in 65% yield on multigram scale. To obtain the core 23-membered ring of virginiamycin M1 (**1**) we used a Stille coupling reaction, the detailed optimization Scheme 1. Scalable synthesis of virginiamycin M1. 1A. Retrosynthetic analysis of virginiamycin M1; 1B. Total synthesis of virginiamycin M1 of which is described in Table 1. Isolated yields are reported, and the variable that was changed in each row is depicted in bold typeface. Initially we tested the most common condition for the intramolecular Stille coupling: $Pd_2(dba)_3$ as a Pd source and $AsPh_3$ as a ligand (when X = I, Br; entry 1 and 2).[21] Unfortunately, these conditions failed to provide detectable amounts of macrocycle **30**. Liebeskind-Stille coupling conditions using CuTC also failed to provide the macrocycle (entry 3).[22] When $Pd(PPh_3)_4$ was used as a catalyst in the presence of LiCl, the Stille product was obtained 15% yield. Next, we screened some more bulky and active catalysts such as $^t Bu_3P$ and Buchwald's biarylposphine ligands. We found that Buchwald's JackiePhos, which was designed to facilitate challenging transmetallation reactions, was found to be optimal (entry 4–10).[23] Furthermore, through optimization of different reaction temperature and several frequently used Pd sources (entry 11, 12, 14–18), the conditions for the highest yield for Stille macrocyclization was confirmed as entry 17. It was noteworthy that there was only trace product formed when Stille precursor (X = I) was used as substrate under similar conditions (entry 13). With the cyclized compound in hand, removal of the silyl groups was accomplished with buffered tetrabutylammonium fluoride to provide virginiamycin M1 (**1**) in 80% yield.[24] Notably, this represented the first fully synthetic route to virginiamycin M1. We next applied our route to the synthesis of virginiamycin M2 (**2**) and the madumycins (**3**, **4**). Importantly, due to the modularity of the route, access to these scaffolds only required modification of the left half coupling partner by means of exchanging the amino acid building block (depicted in green). Since we were able to pool large quantities of the right half (**14**), we did not have to repeat the entire synthesis to access these additional family members. To access virginiamycin M2 (**2**), Mukaiyama aldol product **25** was coupled Fmoc-D-proline (**16**) were coupled without subsequent amine-to-imine oxidation to deliver amine **31** (Scheme 2A). Exposure to right half **14** in the presence of HATU and $^i Pr_2EtN$ to delivered macrocycle precursor **32** in 87% yield. The macrocyclization of compound **32** proceeded smoothly at 50 °C with 20 mol% JackiePhos and 10 mol% $Pd_2(dba)_3$ in 59% yield. Desilylation provided virginiamycin M2 (**2**) in 82% yield. Overall, the route proceeds in 31% yield from **18** and **19** (7 steps) or 18% overall yield from **22** and **23** (6 steps).

To further demonstrate the modularity of our route, we next applied it to the synthesis of madumycin I (**3**) and madumycin II (**4**) as depicted in Scheme 2B. DCC/DMAP-mediated esterification of alcohol **25** with Fmoc-protected D- alanine (**13**) followed by the addition of Et_2NH delivered proline ester **33** in 94% yield. Coupling with the right half (**14**), macrocyclization, and desilylation provided madumycin I (**3**) in yields comparable to those in Scheme 1 and Scheme 2A. Treatment of **3** with sodium borohydride in the presence of diethylmethoxyborane[25] provided madumycin II (**4**) in 72% yield as a single diastereomer. It is noteworthy that this route represented the first reported interconversion of these natural products, and the first total synthesis of madumycin I (**3**).

2. Second generation route to virginiamycin M2

Despite the brevity, modularity and scalability of our first-generation route, it still suffered from contextual limitations including acid sensitivity of intermediates, reliance on toxic organotin reagents (and generation of organotin byproducts), and a moderate-yielding Stille macrocyclization. Thus, we sought to design a shorter, higher-yielding route to virginiamycin M2 (**2**) that overcame these limitations, featuring an unprecedented ene-diene metathesis macrocyclization.

Using our first-generation route as a guideline, the initial efforts toward a second-generation route to virginiamycin M2 (**2**) are summarized in Scheme 3. The synthesis of left half **37** displayed followed the same strategy as the first-generation route, but propargylamine was replaced with allylamine. Notably, this route does not require hydrostannylation, reducing the step count to the left half. The synthesis of left half **37** proceeds from building blocks **18** and **19** in three steps in 81% overall yield, a dramatic improvement of the 42% yield in the first-generation route. The right half synthesis commenced with the aldol coupling of dienal **38a** with chiral auxiliary **23** mediated by a combination of $Sn(OTf)_2$ and *N*-ethylpiperidine instead of $TiCl_4$ and $^{i}Pr_2EtN$, which led to retro-aldol reaction upon quenching with water or pH = 7 phosphate buffer. Silylation of **39a** and cleavage of the thiazolidinethione auxiliary by dianion of oxazole **28** provided right half **41a**. Unlike many alkyl tin species, tin(II) halides do not harbor significant toxicity liabilities, and are included in many household products including toothpaste.[11b]

Precursor **42a** was synthesized by coupling left half 37 with right half **41a** by means of HATU and $^{i}Pr_2EtN$ in 93% yield. To extensively examine the RCM reaction,[26,27] we also prepared precursor **42b**, which contained an additional *trans*-methyl group on the diene function. Initial efforts to cyclize the 23-membered ring of virginiamycin M2 were focused on Grubbs I/II and Hoveyda-Grubbs I/II. Surprisingly, the monosubstituted alkene **42a** (R = H) failed to cyclize under several reaction conditions. However, 15% yield of macrocycle **43** was detected by NMR at ambient temperature with **42b** (R = Me) as a substrate and Hoveyda-Grubbs II as catalyst.

During preliminary experiments, batches of *trans*-methyl diene precursor **42b** were contaminated with small amounts of the corresponding *cis*-methyl precursor (presumably due to impure starting aldehyde **38b**). ^{1}H-NMR analysis of crude RCM reaction mixtures indicated this contaminant was completely consumed even when the majority of **42b** remained unreacted. Thus, we suspected that the *cis*-diene might serve as a more effective precursor for macrocyclization than the *trans*-methyl diene in **42b**.

We were readily able to obtain significant quantities of *cis*-methyl precursor **42c** using stereoisomerically pure dienal **38c** as a starting material (Scheme 4). We found that this served as an effective precursor for macrocyclization in up to 49% yield (see the original publication for a detailed optimization table).[11b] To determine the impact of the silyl groups on the yield of macrocyclization, we treated **42c** with buffered tetrabutylammonium fluoride to provide **42d** in 82% yield. This unprotected precursor underwent macrocyclization to provide virginiamycin M2 (**2**) in 72% yield in presence of Grela II catalyst.[28] Our second-generation route proceeds in 6 steps from 7 simple building blocks in 24–43% overall yield, which is one step shorter and higher yielding than our first-generation route.

Table 2 provides a comparison of our two routes with other previously reported synthetic efforts to natural streptogramin A antibiotics. By leveraging Stille coupling or olefin metathesis to close the 23-membered macrocycle, we were able to prepare the streptogramin A antibiotics in a modular and scalable way with the longest linear sequence (LLS) of 6 – 8 steps (9 – 11 total steps).

3. Conclusion

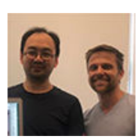
In conclusion, we have developed two modular and concise routes to group A streptogramin antibiotics by assembling 7 simple chemical building blocks in 6–8 linear steps with a high degree of convergency. Each route has proven to be robust and scalable, which facilitates access to sufficient quantities of candidates for both microbiological testing and animal studies. We are currently applying our approach to the syntheses of several non-natural analogs of group A streptogramins with the aims of improving their pharmacological properties, expanding their spectra of activity, and increasing their potency against multidrug-resistant strains of pathogenic bacteria. We have demonstrated that such an approach can yield analogs that overcome streptogramin-specific resistance mechanisms in vitro and in an animal models of infection.[11c] We believe these routes will continue to serve as an engine for discovery of new streptogramin antibiotics, and potentially as a scalable means for their industrial manufacture.

Acknowledgment

Funding Information

This work was supported by the National Institute of General Medical Sciences of the National Institutes of Health (R35GM128656). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Additional support for this work was provided by the David and Lucille Packard Foundation.

Biography



Qi Li (left) received his BS and MS in Medicinal Chemistry from Shenyang Pharmaceutical University under the tutelage of Professor Ping Gong. He completed his PhD with Professor Yian Shi at the Institute of Chemistry in Chinese Academy of the Sciences where he worked on the synthesis of several complex alkaloids. He is currently a postdoctoral fellow with Professor Ian Seiple (right) at UC San Francisco, where he develops fully synthetic routes to several members of the streptogramin class of antibiotics.

References

(1). (a)Centers for Disease Control and Prevention, Office of Infectious Disease Antibiotic resistance threats in the United States, 2013. 4, 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013. Accessed January 28, 2015.(b)Burnham JP; Olsen MA; Kollef MH Infect. Control Hosp. Epidemiol 2019, 40, 112. [PubMed: 30463634]

(2). Waglechner N; Wright GD BMC Biol 2017, 15, 84. [PubMed: 28915805]

(3). Wright PM; Seiple IB; Myers AG Angew. Chem. Int. Ed Engl 2014, 53, 8840. [PubMed: 24990531]

(4). (a)Charney J; Fisher WP; Curran C; Machlowitz RA; Tytell AA Antibiotics and Chemotherapy 1953, 3, 1283. [PubMed: 24542810] (b)Vazquez D In Antibiotics; Gottlieb D, Shaw PD, Eds.; Springer: New York, 1967; Vol. 1, pp 387–403.

(5). (a)Mukhtar TA; Wright GD Chem. Rev 2005, 105, 529. [PubMed: 15700955] (b)Lee VZ, In Comprehensive Medicinal Chemistry II; Taylor JD, Triggle DJ, EDs.; Elsevier: Oxford, 2007; Vol. 7, pp 653–671.

(6). (a)Delgado G Jr.; Neuhauser MM; Bearden DT; Danziger LH Pharmacotherapy 2000, 20, 1469. [PubMed: 11130220] (b)Pavan B Curr. Opin. Invest. Drugs 2000, 1, 173.(c)Bonfiglio G; Furneri PM Expert Opin. Invest. Drugs 2001, 10, 185.(d)Allington DR; Rivey MP Clin. Ther 2001, 23, 24. [PubMed: 11219478]

(7). (a)Politano AD; Sawyer RG Curr. Opin. Invest. Drugs 2010, 11, 225.(b)Pankuch GA; Lin G; Clark C; Appelbaum PC Antimicrob. Agents Chemother. 2011, 55, 1787. [PubMed: 21245439]

(8). Sharkey LKR; O'Neill AJ ACS Infect. Dis. 2018, 4, 239. [PubMed: 29376318]

(9). Leclercq R & Courvalin P Bacterial resistance to macrolide, lincosamide, and streptogramin antibiotics by target modification. Antimicrob. Agents Chemother 1991, 35, 1267 [PubMed: 1929280]

(10). Stogios PJ; Kuhn ML; Evdokimova E; Courvalin P; Anderson WF; Savchenko A Antimicrob. Agents Chemother 2014. 58, 7083. [PubMed: 25223995]

(11). (a)Li Q; Seiple IB J. Am. Chem. Soc 2017, 139, 13304. [PubMed: 28902996] (b)Li Q; Seiple IB Tetrahedron 2019, 75, 3309. [PubMed: 32764837] (c)Li Q; Pellegrino J; Lee DJ; Tran AA; Chaires HA; Wang R; Park JE; Ji K; Chow D; Zhang N; Brilot AF; Biel JT; van Zundert G; Borrelli K; Shinabarger D; Wolfe C; Murray B; Jacobson MP; Mühle E; Chesneau O; Fraser JS; Seiple IB Nature 2020, 586, 145. [PubMed: 32968273]

(12). Schlessinger RH; Li Y-J J. Am. Chem. Soc 1996, 118, 3301.

(13). (a)Tavares F; Lawson JP; Meyers AI J. Am. Chem. Soc 1996, 118, 3303.(b)Dvorak CA; Schmitz WD; Poon DJ; Pryde DC; Lawson JP; Amos RA; Meyers AI Angew. Chem., Int. Ed 2000, 39, 1664.

(14). (a)Wu J; Panek JS Angew. Chem., Int. Ed 2010, 49, 6165.(b)Wu J; Panek JS J. Org. Chem 2011, 76, 9900. [PubMed: 22070230]

(15). (a)Entwistle DA; Jordan SI; Montgomery J; Pattenden G J. Chem. Soc., Perkin Trans 1 1996, 1315.(b)Ghosh AK; Liu W J. Org. Chem 1997, 62, 7908. [PubMed: 11671887] (c)Entwistle DA; Jordan SI; Montgomery J; Pattenden G Synthesis 1998, 1998, 603.(d)Breuilles P; Uguen D Tetrahedron Lett 1998, 39, 3149.

(16). Simsek S; Kalesse M Tetrahedron Lett 2009, 50, 3485.

(17). Ochiai M; Inenaga M; Nagao Y; Moriarty RM; Vaid RK; Duncan MP Tetrahedron Lett 1988, 29, 6917–6920.

(18). (a)Nagao Y, Hagiwara Y; Kumagai T; Ochiai M, Inoue T, Hashimoto K; Fujita EJ Org. Chem 1986, 51, 2391.(b)Romo D; Choi NS; Li S; Buchler I; Shi Z; Liu JO J. Am. Chem. Soc 2004, 126, 10582. [PubMed: 15327314]

(19). Wood RD; Ganem B Tetrahedron Lett 1983, 24, 4391.

(20). Devos A; Remion J; Frisque-Hesbain A-M; Colens A; Ghosez LJ Chem. Soc., Chem. Commun 1979, 1180.

(21). Heravi MM; Hashemi E; Azimian F Tetrahedron 2014, 70, 7.

(22). Liebeskind LS; Fengl RW J. Org. Chem 1990, 55, 5359.

(23). (a)For the structure, synthesis, and initial applications of JackiePhos, see: Hicks JD; Hyde AM; Cuezva AM; Buchwald SL J. Am. Chem. Soc 2009, 131, 16720. [PubMed: 19886610] (b)For applications of JackiePhos in Stille reactions, see: Li L; Wang C-Y; Huang R; Biscoe MR Nat. Chem 2013, 5, 607. [PubMed: 23787752] (c)Zhu F; Rourke MJ; Yang T; Rodriguez J; Walczak MA J. Am. Chem. Soc 2016, 138, 12049. [PubMed: 27612008]

(24). (a)Entwistle DA; Jordan SI; Montgomery J; Pattenden G J. Chem. Soc., Perkin Trans 1 1996, 1315.(b)Ghosh AK; Liu W J. Org. Chem 1997, 62, 7908. [PubMed: 11671887] (c)Entwistle DA; Jordan SI; Montgomery J; Pattenden G Synthesis 1998, 1998, 603.(d)Breuilles P; Uguen D Tetrahedron Lett 1998, 39, 3149.

(25). Chen K-M; Hardtmann GE; Prasad K; Repič O; Shapiro MJ Tetrahedron Lett 1987, 28, 155.

(26). (a)For representative books on RCM:Cossy J; Arseniyadis S; Meyer C Metathesis in Natural Product Synthesis: Strategies, Substrates, and Catalysts.; Wiley-VCH: Weinheim, Germany, 1st ed, 2010;(b)van Lierop BJ, Limmiss JAM, Fogg DE In Olefin Metathesis: Theory and Practice; Grela K, Ed.; John Wiley & Sons: Hoboken, NJ, 2014; chapter 3, pp 85–153;(c)Grubbs RH, Handbook of Metathesis, 3 volume set; Wiley-VCH: Weinheim, 2nd ed., 2015.

(27). (a)For representative reviews on RCM: Grubbs RH; Miller S. J. Miller; Fu GC Acc. Chem. Res 1995, 28, 446.(b)Nicolaou KC, Bulger PG, Sarlah D, Angew. Chem. Int. Ed 2005, 44, 4490. (c)Dhambri CL, Sanogo LAY; Zeghbib R, Othman RB, Lannou M-I, Sprom G; Ardisson J Nat. Prod. Rep 2018, 35, 105. [PubMed: 29345263] (d)Ogba OM, Waner NC, O'Leary DJ, Grubbs RH Chem. Soc. Rev 2018, 47, 4510. [PubMed: 29714397]

(28). (a)Grela K; Harutyunyan S; Michrowska A Angew. Chem., Int. Ed 2002, 41, 4038. (b)Michrowska A; Bujok R; Harutyunyan S; Sashuk V; Dolgonos G; Grela K J. Am. Chem. Soc 2004, 126, 9318. [PubMed: 15281822]

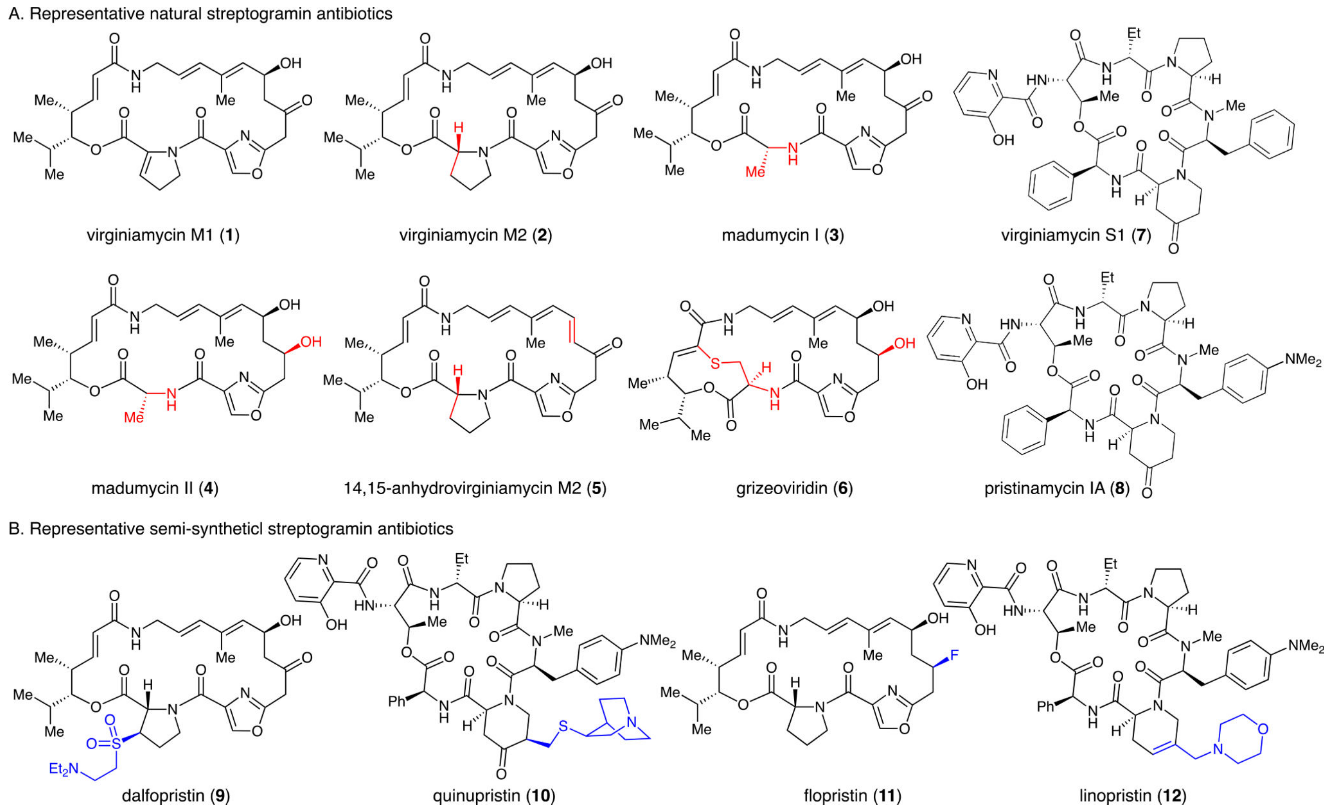
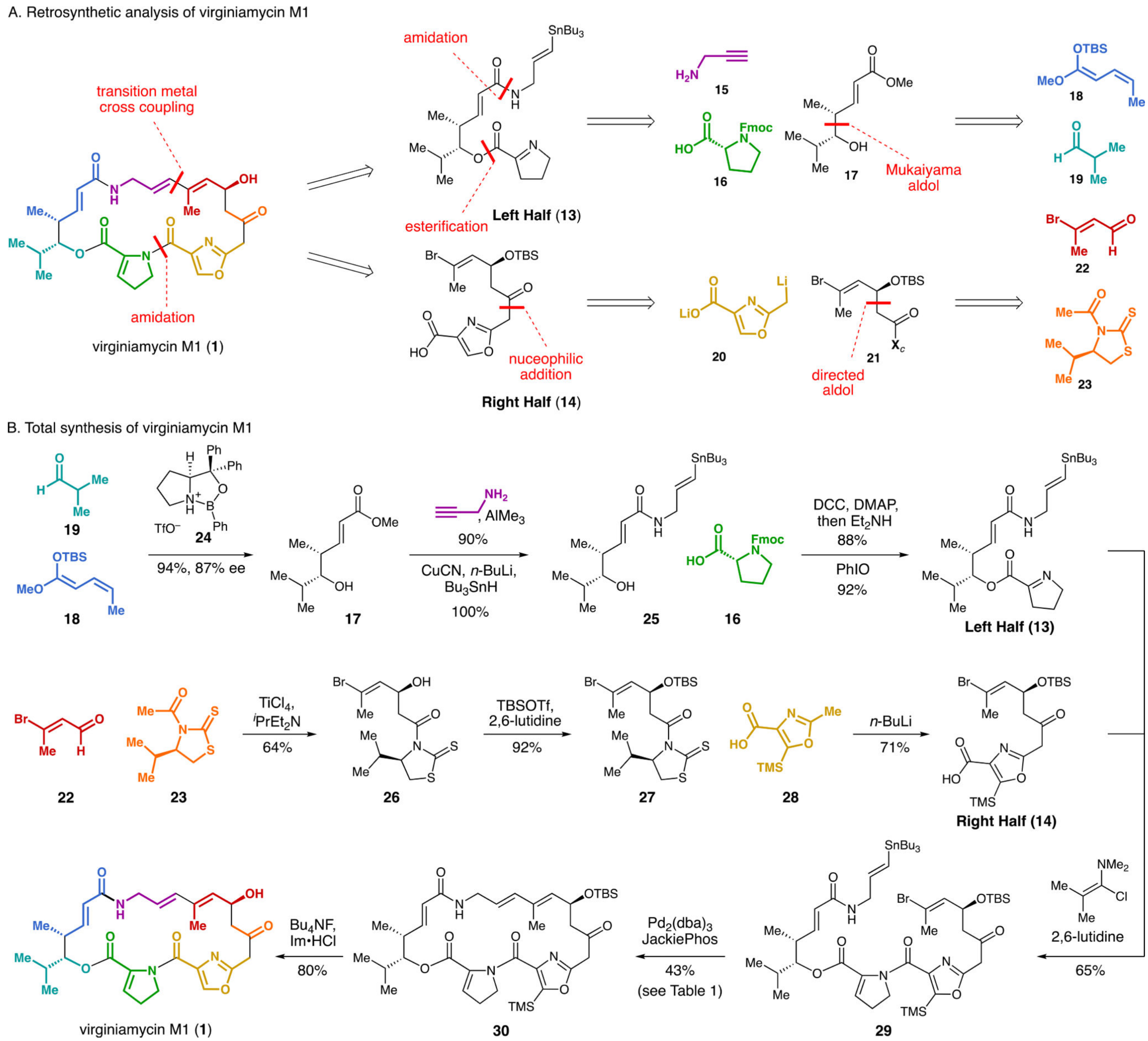


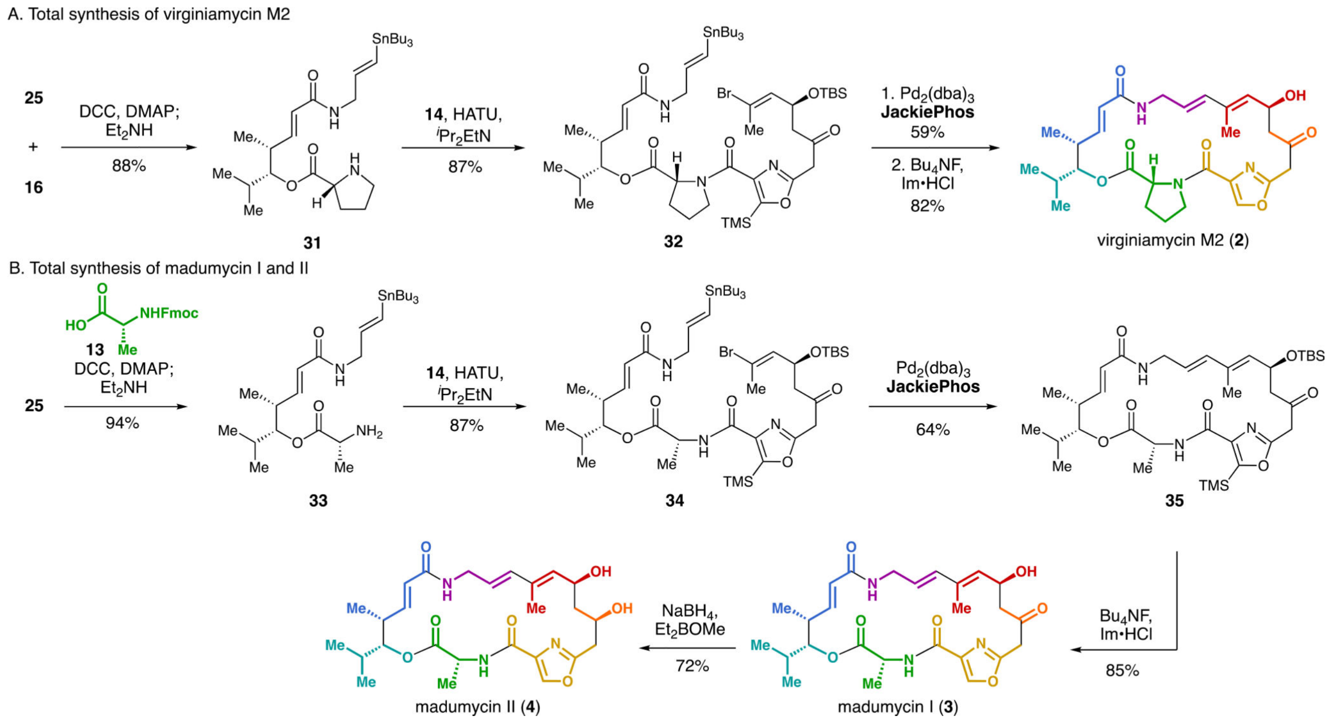
Figure 1.

Streptogramins antibiotics. A. Representative natural streptogramins antibiotics. Variation from virginiamycin M1 is highlighted in red. B. Representative semisynthetic streptogramins. Semisynthetic modifications are highlighted in blue.



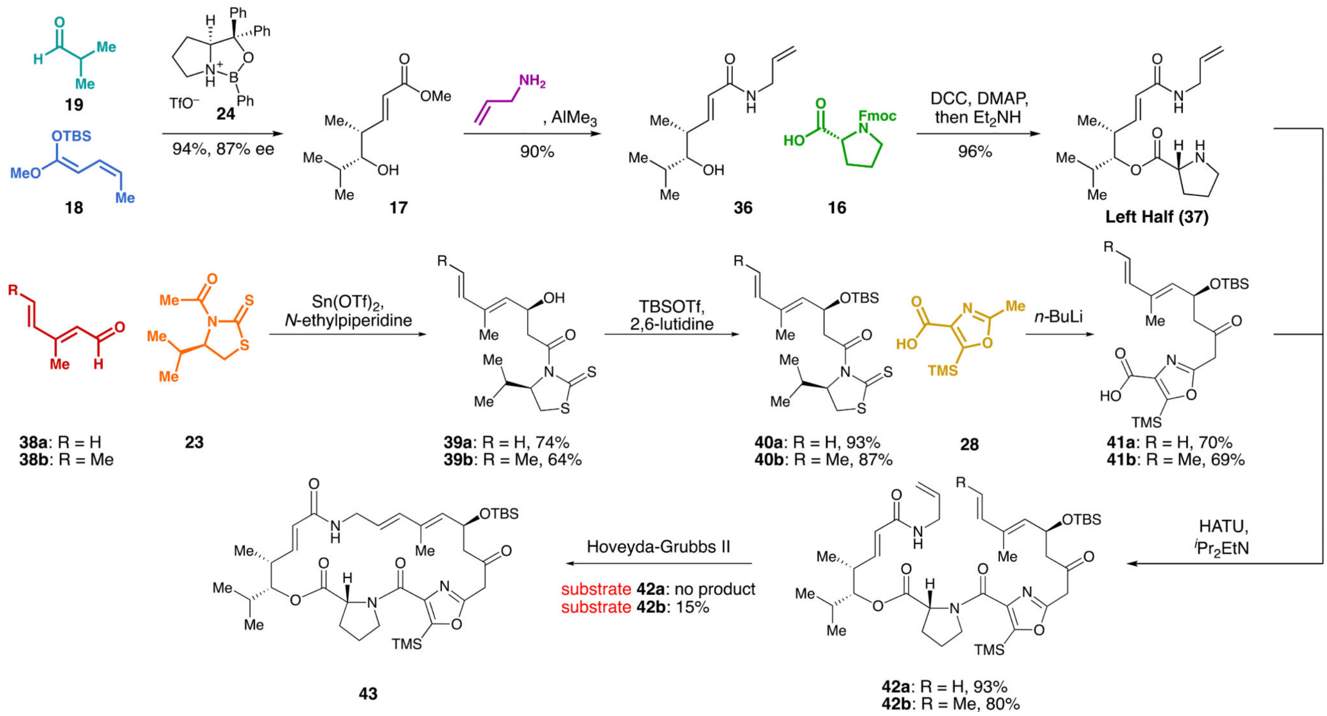
Scheme 1.

Scalable synthesis of virginiamycin M1. 1A. Retrosynthetic analysis of virginiamycin M1; 1B. Total synthesis of virginiamycin M1



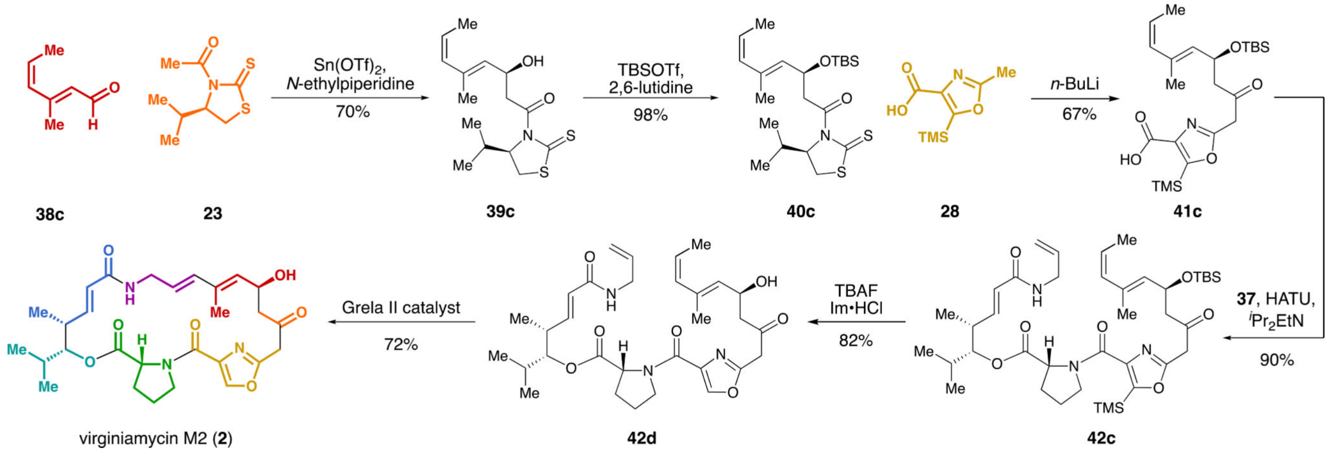
Scheme 2.

Total synthesis of virginiamycin M2, madumycin I and madumycin II. A. Total synthesis of virginiamycin M2; B. Total synthesis of madumycin I and II.



Scheme 3.

Initial efforts of synthesis of virginiamycin M2

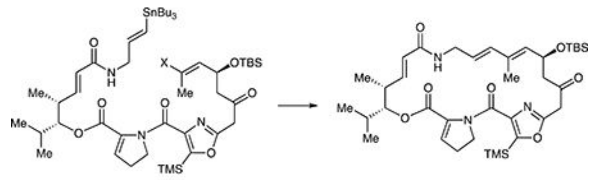


Scheme 4.

Second-generation route to virginiamycin M2.

Table 1.

Optimization of reaction conditions



29 30

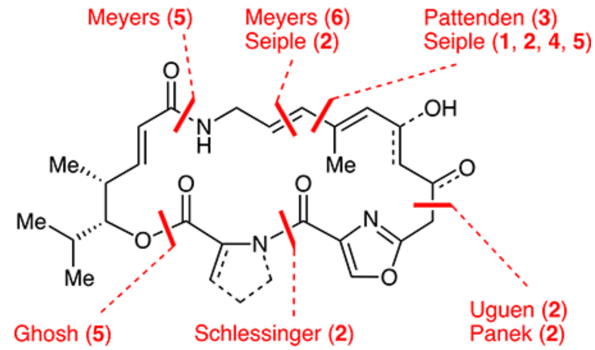
entry	X	ligand (mol%)	Pd source (mol%)	solvent (conc.)	conditions	yield (%)
1	Br	$AsPh_3$ (80)	$Pd_2(dba)_3$ (10 × 2)	THF (2 mM)	80 °C, 72 h	nd
2	I	$AsPh_3$ (80)	$Pd_2(dba)_3$ (10 × 2)	THF (2 mM)	80 °C, 72 h	nd
3[a]	I	-	$Pd(PPh_3)_4$ (10)	DMSO (2 mM)	23 °C, 30 min	nd
4	Br	LiCl (500)	$Pd_2(dba)_3$ (10)	DMF (2 mM)	50 °C, 40 h	nd
5	Br	-	$Pd(PPh_3)_4$ (20)	toluene (2 mM)	50 °C, 40 h	15
6	Br	$^tBu_3P$ (30)	$Pd_2(dba)_3$ (15)	toluene (2 mM)	80 °C, 24 h	19
7	Br	JohnPhos (30)	$Pd_2(dba)_3$ (15)	toluene (2 mM)	80 °C, 24 h	14
8	Br	RuPhos (30)	$Pd_2(dba)_3$ (15)	toluene (2 mM)	80 °C, 24 h	31
9	Br	BrettPhos (30)	$Pd_2(dba)_3$ (15)	toluene (2 mM)	80 °C, 24 h	39
10	Br	**JackiePhos (30)**	$Pd_2(dba)_3$ (15)	toluene (2 mM)	**80 °C, 24 h**	43
11	Br	JackiePhos (30)	$Pd_2(dba)_3$ (15)	toluene (2 mM)	**50 °C, 72 h**	34
12	Br	JackiePhos (30)	$Pd_2(dba)_3$ (15)	toluene (2 mM)	**110 °C, 24 h**	30
13	I	JackiePhos (30)	$Pd_2(dba)_3$ (15)	toluene (2 mM)	**80 °C, 24 h**	20
14	Br	**JackiePhos-Pd-G3 (30)**		toluene (2 mM)	80 °C, 24 h	42
15	Br	JackiePhos (40)	**[π-allyl-Pd-Cl]$_2$ (10)**	toluene (2 mM)	50 °C, 72 h	27
16	Br	JackiePhos (50)	**$Pd(OAc)_2$ (20)**	toluene (2 mM)	50 °C, 72 h	nd
17	Br	JackiePhos (30)	$Pd_2(dba)_3$ (15)	**toluene (10 mM)**	80 °C, 24 h	43
18	Br	JackiePhos (30)	$Pd_2(dba)_3$ (15)	**toluene (50 mM)**	80 °C, 24 h	nd

[a] CuTC (1.5 equiv) was added for Liebeskind-Stille coupling.

Table 2.

Comparison of reported synthetic route to natural streptogramin A antibiotics

Macrocyclization Locations and (Targets)



Route Comparators

Target	Group	Total Steps	Longest Linear Sequence	Macrocyclization Reaction	Macrocyclization Yield	Overall Yield
virginiamycin M1 (**1**)	Seiple	11	6, 8	Stille Coupling	43%	9 – 15%
virginiamycin M2 (**2**)	Schlessinger	22	17	Lactamization	52%	2.8%
	Uguen	48	28	Takai Coupling	23%	<0.2%
	Panek	19	10	Barbier Coupling	42%	6%
	Seiple	10	6, 7	Stille Coupling	59%	18 – 31%
	Seiple	9	6	RCM	72%	24 – 43%
14,15-anhydro-VM2 (**3**)	Pattenden	23	13	Stille Coupling	30%	2.3 – 2.8%
madumycin I (**4**)	Seiple	10	6,7	Stille Coupling	64%	15 – 27%
madumycin II (**5**)	Meyers	28	23	Lactamization	32%	1.8%
	Ghosh	32	27	Lactonization	63%	0.68%
	Seiple	11	7, 8	Stille Coupling	64%	15 – 27%
griseoviridin (**6**)	Meyers	32	24	RCM	37 – 42%	2.5 – 3.5%