Natural Product Synthesis

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Total Synthesis of (−)-Virginiamycin M_2**

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The virginiamycins are naturally occurring antibiotics produced by *Streptomyces*, comprised of two principle groups of compounds (types A and B; Figure 1). The realization that

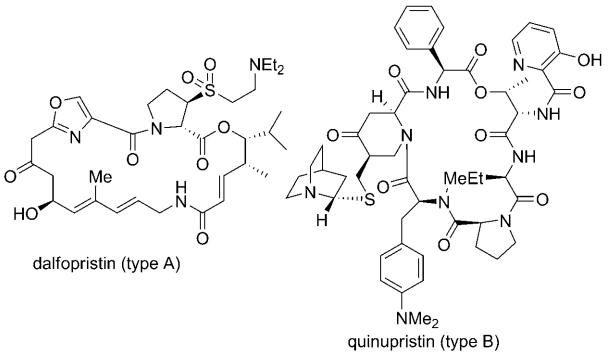
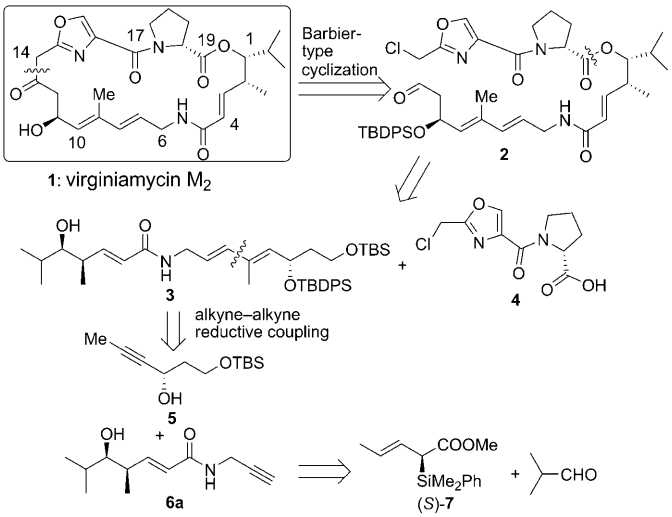


Figure 1. Synercid (dalfopristin + quinupristin).

natural and synthetic derivatives of virginiamycins have displayed potent antibiotic activity against methicillin-, erythromycin-, and vancomycin-resistant *S.aureus*,[1] by inhibiting protein synthesis through synergistic binding of weak ribsome binders, has resulted in an active research area in both academia and industry.[2,3] These efforts resulted in the development of Synercid (Figure 1), a mixture of dalfopristin (type A) and quinupristin (type B), which was approved in the United States for the treatment of severe Gram-positive bacterial infections a little over a decade ago.[4] However, production of dalfopristin-like compounds by semisynthesis has been hampered by their sensitive functionalities and pH instability.[2] Herein, we report a concise and modular total synthesis of virginiamycin M_2, a typical member of virginiamycin group A compounds originally isolated by Todd and co-workers.[5]

Our strategy for the synthesis of virginiamycin M_2 is illustrated in Scheme 1, where we envisioned formation of the 23-membered macrocycle through a SmI_2-mediated intramolecular Barbier/Reformatsky-type cyclization[6] from the acyclic framework **2**. This material could be accessed by means of esterification of the homoallylic alcohol **3** and the proline intermediate **4**. The (*E*,*E*)-diene subunit **3** could be obtained through an efficient pathway; by using a titanium-mediated reductive alkyne–alkyne cross-coupling between the propargylic alcohol **5** and terminal alkyne **6a**,[7] which could be conveniently introduced through crotylation utilizing the organosilane (*S*)-**7**. This silane reagent has unique features as it establishes the C1−C2 *syn* stereochemistry while



Scheme 1. Retrosynthetic analysis of virginiamycin M_2. TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

simultaneously creating the C3−C5 (*E*)-unsaturated ester subunit, thereby functioning as a vinylogous aldol reagent.[8]

Construction of the terminal alkyne **6a** began with an asymmetric crotylation between (*S*)-**7** and isobutyraldehyde to directly obtain the vinylogous-aldol product **8** as a single diastereomer with 95% *ee* (Scheme 2A).[9] The organosilane (*S*)-**7** was obtained through an enantioselective carbene insertion catalyzed by Rh^{II} with the *ee* value reaching 95%.[10] The ester **8** was subjected to Weinreb's amidation with propargylamine in the presence of $AlMe_3$ to afford the amide **6a**. To achieve the C9–C13 fragment, the propargylic alcohol **5** was prepared from known aldehyde **10** (two steps from commercial 1,3-propandiol **9**)[11] using the Carreira

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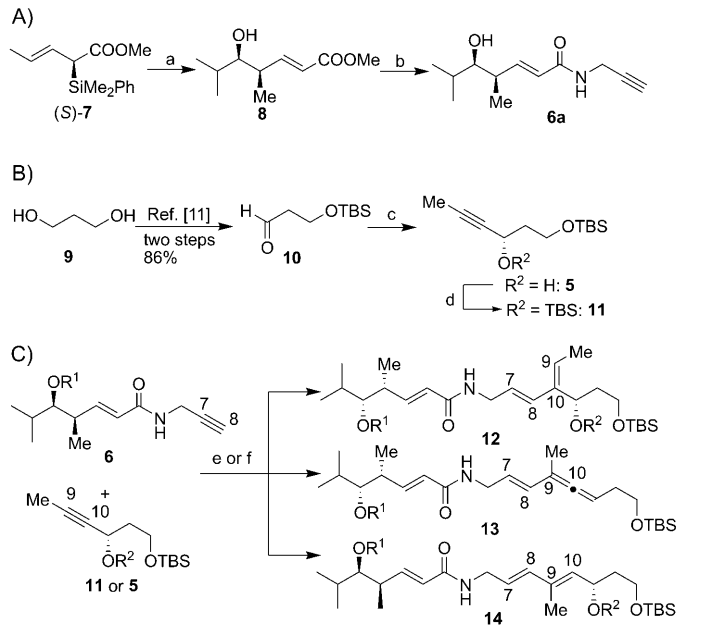
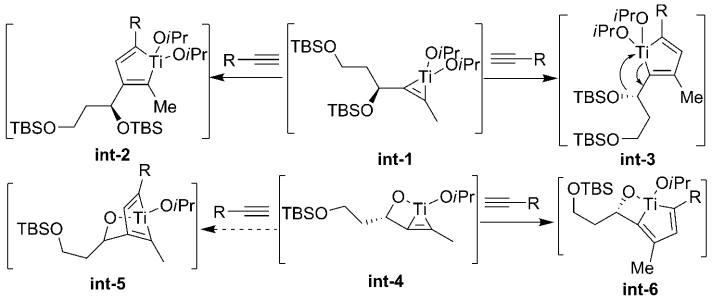


Entry	terminal alkyne **6**	internal alkyne	condition	yields		
				12	**13**	**14**
1	**6b**: R^1= Bn	**11**	e	**12a** (45%)	**13a** (19%)	**14a** (0%)
2	**6c**: R^1= Ac	**11**	e	**12b** (49%)	**13b** (39%)	**14b** (0%)
3	**6c**: R^1= Ac	**5**	f	**12c** (0%)	**13c** (0%)	**14c** (71%)
4	**6a**: R^1= H	**5**	f	**12d** (0%)	**13d** (16%)	**14d** (58%)



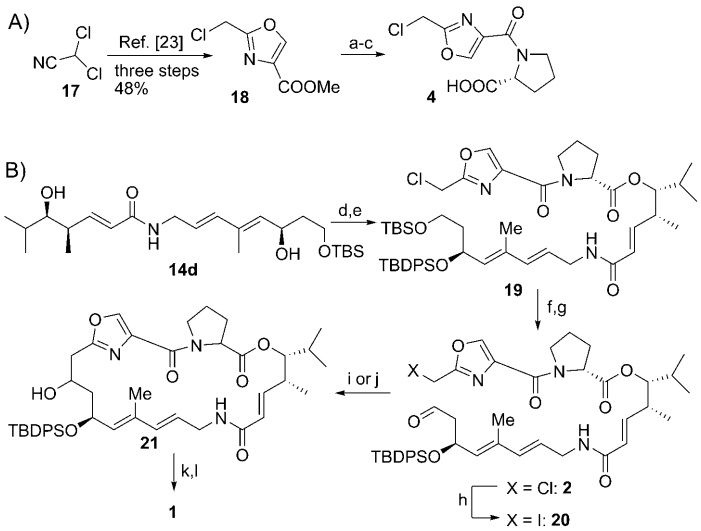
Scheme 2. A) Synthesis of C1–C8 fragment: a) Isobutyraldehyde, $TiCl_4$, CH_2Cl_2, −20 °C, 63 %, d.r. > 20:1, 95 % *ee*; b) $AlMe_3$, propargylamine, 87 %. B) Synthesis of C9–C13 fragment: c) $Zn(OTf)_2$, (−)-*N*-methylephedrine, propyne, Et_3N, 80 %, 95 % *ee*; d) TBSOTf, 2,6-lutidine, 96 %. C) Alkyne–alkyne reductive coupling: e) $Ti(OiPr)_3Cl$, cyclopentyl magnesium chloride, toluene, −78 °C to −30 °C; f) *n*BuLi, $Ti(OiPr)_3Cl$, cyclopentyl magnesium chloride, Et_2O, −78 °C to −30 °C. The reported yields are those for the product isolated after column chromtography. The yields reported for entry 4 are based on recovered starting material. OTf = trifluoromethanesulfonate, TBS = *tert*-butyldimethylsilyl.

protocol[12] and subsequent silylation with TBSOTf to afford the propargylic ether **11** (Scheme 2 B). Asymmetric addition using Carreira's protocol proceeded efficiently with propyne, and without evidence of self-aldol condensation of the starting aldehyde.

With the two alkyne reaction partners now available, our next objective was to assemble the conjugated diene fragment **14**. Although there were several options available for the construction of branched conjugated dienes,[13] we were interested in the use of a titanium-mediated reductive cross-coupling strategy, which would lead directly to the intermediate **14** without the requirement of generating preactivated and stereodefined olefinic coupling partners. In that regard, Micalizio and co-workers employed a related approach in the synthesis of callystatin A by using a homopropargylic ether.[7b] However, in the present case, the coupling of the propargylic ether **11** with a terminal alkyne did not afford the desired diene **14** (Scheme 2 C, entries 1 and 2); instead, only the regioisomer **12** and allene **13** were isolated. We envisioned that the in situ generated internal alkyne–titanium complex **int-1**[14] was allowed to undergo carbometallation with the terminal alkyne presumably through **int-2** and **int-3** to afford **12** and **13** respectively,[15] as functionalization of the terminal alkyne substrate generally occurred at the terminal carbon atom of the alkyne.[16] Notably, instead of forming the trisubstituted diene after hydrolysis, the corresponding allene compounds **13** were generated presumably through β elimination of the OTBS group in **int-3** (Scheme 2).[17] To overcome the influence of the propargylic ether, we planned to evaluate the directing ability of the secondary hydroxy group in **5** since there was a possibility that the proximal heteroatom (hydroxy group) would coordinate with the neighboring metal center.[18] The reactions were initiated by preforming the lithium oxide using *n*BuLi,[19] which would undergo ligand exchange with titanium[20] to produce lithium isopropoxide, and lead to the presumed metallacyclopropene intermediate **int-4**.[21] If the structure of tethered alkoxide **int-4** was retained during the C–C bond formation, it would preferentially afford the metallacyclopentadiene intermediate **int-6**, since **int-5** would encounter significant strain when forming the bridgehead alkene.[21] Although the coordination of alkoxide with titanium was expected to exhibit considerable ring strain in the bicyclic metallacyclopropene **int-4**,[21a] diene **14c** was obtained with excellent regioselectivity and good yield (entry 3), and without detection of by-products **12c** or **13c**. The terminal alkyne **6** also reacted in a regioselective manner to give the desired diol product **14d** (entry 4), which was accompanied by a small amount of allene by-product **13d**.[22]

The synthesis of the C14–C19 subunit (Scheme 3 A) commenced with hydrolysis of the oxazole ester **18**,[23] and subsequent coupling with D-proline benzyl ester hydrochloride. A subsequent Lewis acid promoted cleavage of the benzyl ester provided amide subunit **4** as a 3:1 mixture of rotamers.

In making use of the difference in the steric environment of the two secondary hydroxy groups in **14d**, the C11 hydroxy group was selectively silylated as a TBDPS ether **3**. Subsequent fragment coupling with **4** proceeded efficiently under the Yamaguchi condition[24] to yield **19** as a mixture of 1:1 rotamers (Scheme 3 B). The final stages of the synthesis began with the selective removal of the primary silyl group of **19**, and oxidation of the derived primary alcohol using IBX afforded the advanced aldehyde **2**.[3b] Treatment of the chloroaldehyde



Scheme 3. A) Synthesis of the C14—C19 subunit: a) LiOH, THF/H_2O (4:1), 95%; b) EDCI·HCl, (*R*)-NH(HCl)-Pro-OBn, Et_3N, 80%; c) BCl_3, −20°C to 0°C, 70%. B) Completion of the synthesis: d) TBDPSCl, imidazole, 0°C, 92%; e) **4**, 2,4,6-trichlorobenzoyl chloride, benzene, DIPEA, DMAP, 86%; f) CSA, CH_2Cl_2, MeOH, 0°C, 62% (85% brsm); g) IBX, DMSO, 92%; h) NaI, acetone, 95%; i) SmI_2, benzene, **2**, 40%; j) SmI_2, benzene, **20**, 42%; k) TFAA, DMSO, CH_2Cl_2, −78°C to −45°C, acetylacetone, Et_3N, −60°C to −35°C, 84%; l) HF·2pyridine, CH_2Cl_2, 70%. THF = tetrahydrofuran, EDCI = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide, DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, CSA = (±)-camphorsulfonic acid, IBX = *ortho*-iodoxybenzoic acid, DMSO = dimethyl sulfoxide, TFAA = trifuoroacetic acid.

2 with NaI in acetone provided iodide **20** in 95% yield. At this stage we were faced with the challenge of closing the 23-membered macrocycle and our initial experiments were unsuccessful. For instance, exposure of the advanced intermediate **20** to a THF solution of freshly prepared SmI_2[6c] led to a disappointing yield (approximately 10%) of the desired macrocyclic lactone **21**, with the majority identified as the reduced aldehyde and deiodinated material. The lower yield (<5%) obtained from highly dilute THF solution (0.002 M) indicated that the initially formed benzylic-like radical abstracted a hydrogen atom from THF, thus preventing the generation of the desired organosamarium intermediate.[25] The desired product was isolated in moderate yield (42%) as a 1:1 diastereomeric mixture when benzene was used as the reaction solvent. The less reactive chloromethyloxazole **2** underwent cyclization with similar yield. To the best of our knowledge, this is the first example of a SmI_2-mediated macrocyclization that uses benzene to suppress the competitive dehalogenation pathway. Subsequent oxidation of the resulting secondary alcohol using a modified TFAA/DMSO Swern procedure yielded the corresponding ketone in good yield. The addition of acetylacetone was used to help prevent further enolization of the ketone product.[26] Final removal of the C11 TBDPS ether using pyridine buffered HF gave virginiamycin M_2 in 70% yield. The spectral data and analytical data (^{1}H and ^{13}C NMR, IR, HRMS, optical rotation) were identical with the published data.[3a]

In summary, virginiamycin M_2 (**1**) has been synthesized in 19 steps with the longest linear sequence of 10 steps from silane (*S*)-**7** in a 6.0% overall yield. Notable features of our approach include the application of chiral silane (*S*)-**7** for the asymmetric synthesis of the *syn* vinylogous aldol product, use of an alkoxide-directed reductive coupling to construct the (*E*,*E*)-diene, and a SmI_2-promoted Barbier-type cyclization, which afforded the largest macrocycle (23-membered) among SmI_2 mediated macrocyclizations to date.[6]

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