Total Synthesis

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Total Synthesis and Structural Revision of Viridicatumtoxin B**

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The discovery and development of antibiotics in the first half of the 20th century revolutionized medicine and led to a dramatic enhancement of life expectancy.[1] However, the emergence of drug-resistant bacterial strains caused by the extensive use of antibiotics in both humans and livestock risks rendering the world's arsenal of antibiotics ineffective.[2] The development of novel antibacterial agents is, therefore, of high priority.

The nefarious molecular architectures of tetracyclines have challenged synthetic chemists for over six decades,[3] with impressive results being reported most recently from the Myers research group.[4] Structurally related to the tetracycline antibiotics are the viridicatumtoxins (**1**–**3**, Figure 1), which constitute an intriguing subclass of naturally occurring potent antibacterial agents. Originally isolated in 1973 from a *Penicillium* species,[5] viridicatumtoxin A (**1**) was structurally elucidated through the aid of X-ray crystallographic analysis in 1976.[6] In 2008, Kim and co-workers reported the re-isolation of viridicatumtoxin A (**1**) as well as the isolation of viridicatumtoxin B, whose structure was assigned as **2** (Figure 1).[7] Finally, spirohexaline (**3**) was reported in early 2013.[8] Viridicatumtoxins A (**1**) and B (**2**) were shown to exhibit antibacterial activity against a variety of Gram-positive bacterial strains, including methicillin-resistant *Staphylococcus aureus* (MRSA) [MIC = 0.25 and 0.5 $\mu g\,mL^{-1}$, respectively; compare tetracycline (**4**, Figure 1) and vancomycin: MIC = 8 and 0.25–1 $\mu g\,mL^{-1}$, respectively].[7] Their mode of action was implied to involve disruption of bacterial peptidoglycan biosynthesis through inhibition of UPP synthase.[9] Despite their impressive antibacterial activities, no synthetic approaches toward the viridicatumtoxins have been reported to date.

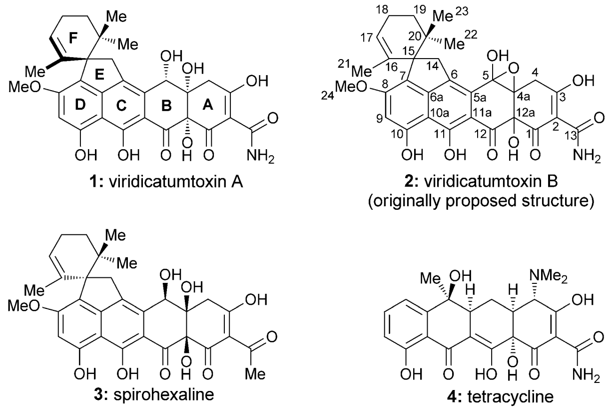

Figure 1. Molecular structures of viridicatumtoxin A (**1**), B (**2**), spirohexaline (**3**), and tetracycline (**4**).

Inspired by the structural complexity, the incomplete and curious structural assignment containing an epoxy hemiacetal structural motif, and potent antibiotic properties of viridicatumtoxin B (**2**), we embarked on its total synthesis. Our objectives were to fully elucidate the structure of viridicatumtoxin B (**2**) and establish the foundation for the synthesis and biological evaluation of designed analogues within this family of antibiotics. A number of distinct structural features add significantly to the challenge of synthesizing viridicatumtoxin B (**2**) compared to the tetracyclines (e.g. **4**, Figure 1). These features include the EF spirosystem of viridicatumtoxin B, its hindered quaternary carbon center at C15, its highly oxidized AB ring system, and the extensive substitution on the ABCD tetracyclic core of the molecule. On the basis of biosynthetic considerations[10] and the known structure of viridicatumtoxin A (**1**),[6] we tentatively assigned the relative configuration of viridicatumtoxin B (**2**) as shown in Figure 2. Our highly convergent strategy toward **2** was derived from the retrosynthetic analysis shown in Figure 2. Thus, disconnection of the indicated six carbon–carbon bonds through the reactions shown revealed four key building blocks: allylic bromide **5**, cyclic anhydride **6**, quinone monoketal **7** (known),[11] and isoxazole phenyl ester **8**. Their construction and assimilation into the targeted molecule would involve three cyclizations (as indicated in Figure 2), the extrusion of

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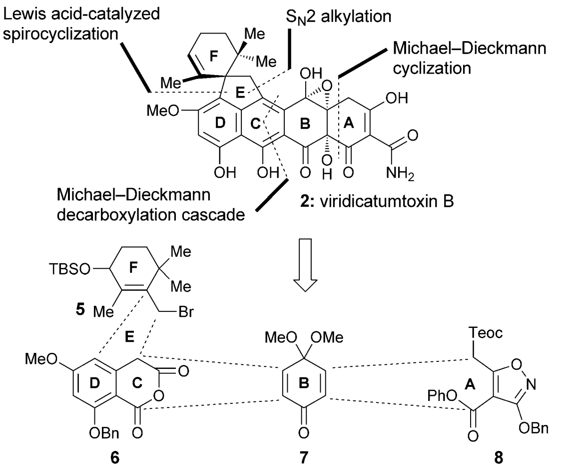
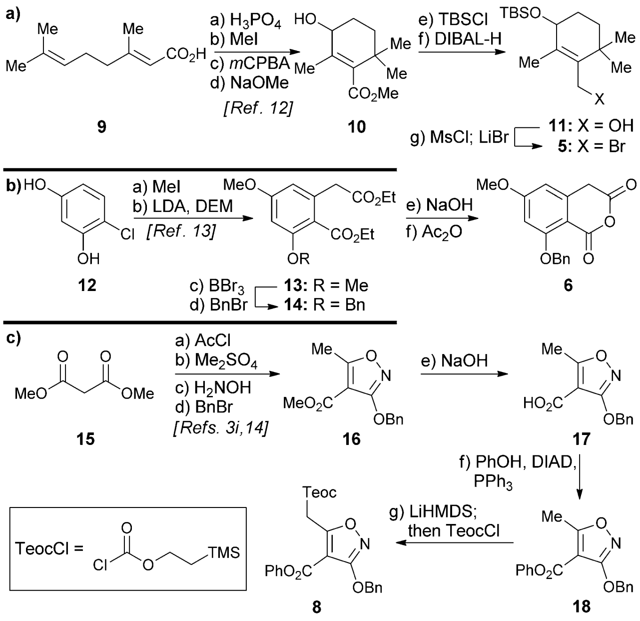


Figure 2. Retrosynthetic analysis of viridicatumtoxin B (**2**). Bn = benzyl, TBS = *tert*-butyldimethylsilyl, Teoc = 2-(trimethylsilyl)ethoxycarbonyl.

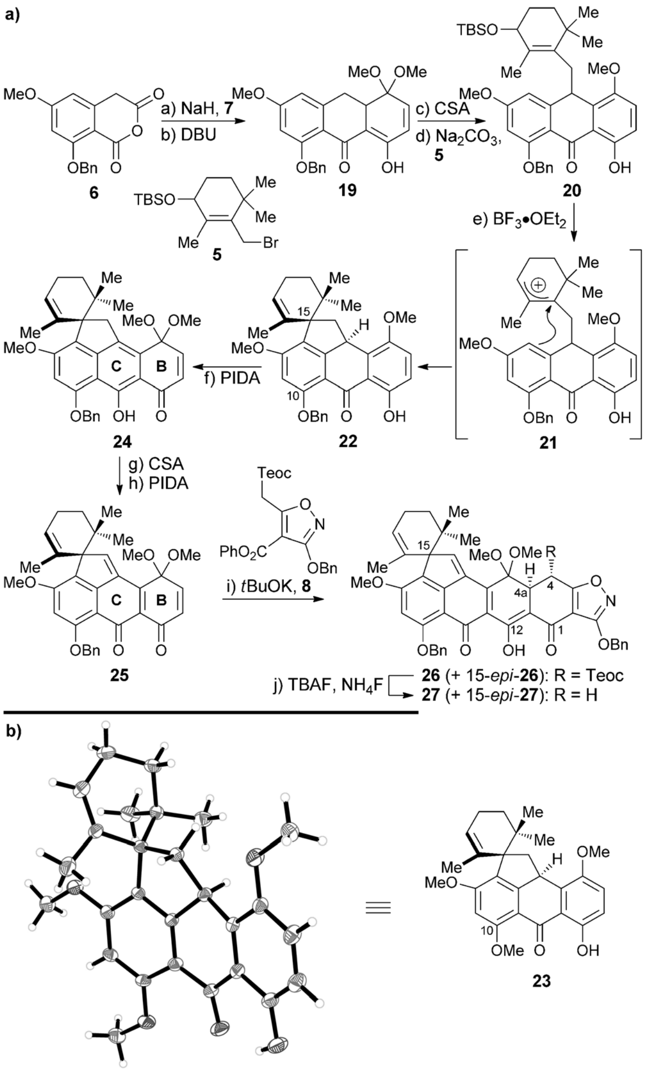


Scheme 1. **a**) Synthesis of allylic bromide **5**; **b**) synthesis of cyclic anhydride **6**; and **c**) synthesis of isoxazole **8**. Reagents and conditions: **a**) a) H_3PO_4 (0.2 equiv), toluene, reflux, 90 min; b) MeI (3.9 equiv), K_2CO_3 (2.0 equiv), acetone, 25 °C, 15 h; c) *m*CPBA (1.2 equiv), CH_2Cl_2, 0→25 °C, 3 h; d) NaOMe (1.5 equiv), MeOH, reflux, 17 h, 70% yield over 4 steps; e) TBSCl (1.6 equiv), imidazole (2.0 equiv), CH_2Cl_2, 25 °C, 12 h; f) DIBAL-H (2.7 equiv), CH_2Cl_2, −78→0 °C, 70 min, 91 % over 2 steps; g) Et_3N (2.0 equiv), MsCl (1.7 equiv), CH_2Cl_2, −50 °C, 1 h; then LiBr (3.5 equiv), THF, −50→−20 °C, 1 h, quant.; **b**) a) MeI (4.0 equiv), K_2CO_3 (8.0 equiv), acetone, reflux, 15 h, 91 %; b) NaH (6.0 equiv), DEM (4.0 equiv), THF, 0 °C, 2.5 h; then LDA (1.0 equiv), THF, 0 °C, 3.5 h, 65 %; c) BBr_3 (1.35 equiv), CH_2Cl_2, −78→25 °C, 30 min; d) BnBr (1.1 equiv), Ag_2O (1.9 equiv), DMF, 25 °C, 15 h, 66 % over 2 steps; e) NaOH (27 equiv), H_2O/EtOH 5:7, reflux, 15 h; f) Ac_2O (1.1 equiv), toluene, reflux, 1 h, 90 % over 2 steps; **c**) a) $MgCl_2$ (1.0 equiv), Et_3N (2.0 equiv), AcCl (1.0 equiv), MeCN, 0→25 °C, 23 h, 96 %; b) Me_2SO_4 (1.3 equiv), K_2CO_3 (1.3 equiv), DMF, 0→25 °C, 17 h, 54 %; c) $H_2NOH{\cdot}HCl$ (1.4 equiv), NaOMe (3.1 equiv), MeOH, 0→25 °C, 24 h, 48 %; d) BnBr (1.2 equiv), Ag_2O (1.5 equiv), DMF, 25 °C, 18 h, 67 %; e) NaOH (1.9 equiv), H_2O/EtOH 3:10, 25 °C, 3 h, 99 %; f) PPh_3 (1.05 equiv), PhOH (1.05 equiv), DIAD (1.05 equiv), THF, reflux, 3 h, 78 %; g) LiHMDS (2.2 equiv), THF, −78 °C, 30 min; then TeocCl (2.2 equiv), −78 °C, 2 h, 86 %. *m*CPBA = *meta*-chloroperoxybenzoic acid, DIBAL-H = diisobutylaluminum hydride, Ms = methanesulfonyl, DEM = diethylmalonate, LDA = lithium diisopropylamide, DMF = dimethylformamide, DIAD = diisopropylazodicarboxylate, PhOH = phenol, THF = tetrahydrofuran, LiHMDS = lithium hexamethyldisilazide.

carbon dioxide (from **6**), and the rupture of the isoxazole ring (**8**).

The construction of building blocks **5**, **6**, and **8** is summarized in Scheme 1. The synthetic route to allylic bromide **5**, the precursor for the EF spirocyclic ring system, commenced with a modification of a known, four-step sequence to convert geranic acid (**9**) into methyl ester allylic alcohol **10** (Scheme 1 a).[12] Silylation (TBSCl, imidazole) of **10** followed by ester reduction (DIBAL-H) produced allylic alcohol **11** in 91 % overall yield. Low-temperature mesylation of the latter (MsCl, Et_3N) followed by displacement of the resulting mesylate moiety with LiBr produced the desired fragment **5** in quantitative yield (Scheme 1 a). Synthesis of the cyclic anhydride **6** commenced from intermediate **13** [available in two steps from 4-chlororesorcinol (**12**) by a literature procedure, Scheme 1 b].[13] Selective mono-demethylation of **13** (directed by the nearby ester moiety on the aromatic ring) was achieved through the use of BBr_3. Reprotection of the liberated phenolic group to give intermediate **14** was accomplished using Ag_2O/BnBr (66 % yield for 2 steps). Saponification (aq NaOH) and anhydride formation (Ac_2O) produced the desired cyclic anhydride **6** (90 % yield over 2 steps). The synthesis of isoxazole fragment **8** commenced from known Stork–Hagedorn isoxazole **16**[3i,14] (Scheme 1 c), which was prepared by a modified literature process involving sequential acylation of dimethylmalonate (AcCl, Et_3N, $MgCl_2$, 96 % yield),[15] methylation of the resulting enol (Me_2SO_4, K_2CO_3, 54 % yield), cyclization ($H_2NOH{\cdot}HCl$, NaOMe, 48 % yield), and subsequent benzylation of the free hydroxy group (BnBr, Ag_2O, 67 % yield). Saponification of the so-produced methyl ester then furnished carboxylic acid **17** (aq NaOH, 99 % yield). Conventional esterification methods to prepare the phenyl ester **18**, such as through the intermediacy of the corresponding chloride or the mixed anhydride, failed, as did the use of peptide coupling reagents. The desired phenyl ester formation, however, could be achieved under Mitsunobu conditions (PPh_3, PhOH, DIAD, 78 % yield).[16] The need to install an electron-withdrawing—and ideally easily removable—group at the isoxazole methyl group was predicated on AB ring model systems; such a group was found to be required to facilitate a later conjugate addition. To this end, deprotonation of the methyl group of phenyl ester **18** (LiHMDS) and quenching of the resulting anionic species with TeocCl produced the desired fragment **8** (86 % yield). Quinone monoketal **7** was readily available in one step by a literature procedure.[11]

With all four building blocks (**5**–**8**) in hand, the stage was now set for their union, as shown in Scheme 2 a. Annulation of cyclic anhydride **6** with quinone monoketal **7** to afford tricyclic compound **19** was achieved by using a one-step Michael–Dieckmann/decarboxylation protocol (DBU, 65 °C,



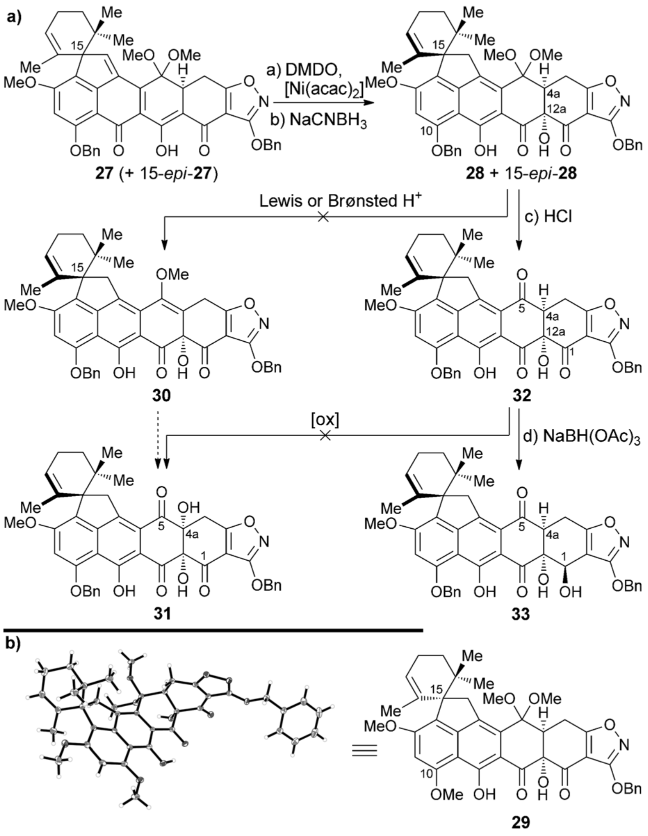
Scheme 2. **a**) Synthesis of heptacycle **27** and **b**) ORTEP representation of spirocycle **23** (thermal ellipsoids at 30% probability; gray = C, red = O, green = H). Reagents and conditions: a) **7** (3.0 equiv), NaH (3.0 equiv), THF, 0 °C, 45 min; then 25 °C, 1 h; b) DBU (5.0 equiv), toluene, 65 °C, 4.5 h, 54% over 2 steps; c) CSA (0.02 equiv), CH_2Cl_2, 25 °C, 30 min, 99%; d) **5** (1.1 equiv), Na_2CO_3 (10 equiv), DMF, 25 °C, 1 h, 77%, d.r. ca. 1:1; e) $BF_3\cdot OEt_2$ (0.15 equiv), CH_2Cl_2, 0 °C, 20 min, 73%; f) PIDA (1.2 equiv), $MeOH/CH_2Cl_2$ 1:1, $0\rightarrow25$ °C, 1 h; g) CSA (0.07 equiv), CH_2Cl_2, 0 °C, 5 min, 85% over 2 steps; h) PIDA (1.2 equiv), $MeOH/CH_2Cl_2$ 10:1, 25 °C, 1.5 h, 90%; i) **8** (1.1 equiv), *t*BuOK (1.2 equiv), toluene, 25 °C, 15 min, 91%, d.r. ca. 2:1; j) TBAF (10 equiv), NH_4F (20 equiv), degassed THF, 25 °C, 5 min, 86%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, CSA = (±)-camphor-10-sulfonic acid, PIDA = iodobenzene diacetate, TBAF = tetra-*n*-butylammonium fluoride.

41% yield). However, a two-step protocol involving exposure of **6** and **7** to NaH to induce anion generation and cycloaddition followed by work-up and subsequent treatment with DBU to promote decarboxylation was preferred, as it proved more efficient in producing **19** (54% yield overall).[17] Reaction of ketal **19** with catalytic amounts of CSA caused extrusion of methanol, thereby furnishing the corresponding anthrone (99% yield), whose alkylation with allylic bromide **5** proceeded under mild basic conditions (i.e. Na_2CO_3) to give intermediate **20** (77% yield, d.r. ca. 1:1). Much to our delight, ionization of the allylic TBS ether was readily achieved with catalytic quantities of $BF_3\cdot OEt_2$, presumably forming highly stabilized but fleeting allylic cation **21**, whose intramolecular trapping by the nearby electron-rich arene led to spirocycle **22** as a single diastereomer (73% yield). The connectivity and relative stereochemical relationships within pentacycle **22** were assigned by comparing its NMR spectroscopic data with those of the related compound **23** (10-methoxy as opposed to 10-benzyloxy, Scheme 2b), whose structure was secured through X-ray crystallographic analysis [m.p. = 114–116 °C ($CHCl_3$/EtOAc), see ORTEP representation, Scheme 2b].[18]

To ready the newly acquired pentacycle **22** for cyclization with isoxazole **8**, and thus forge ring A of the growing molecule, the former was treated with $PhI(OAc)_2$ (PIDA, phenolic oxidation) to produce B-ring enone **24**, which, however, did not undergo the desired Michael–Dieckmann reaction with isoxazole **8**. We hypothesized that this reluctance was due to the adjacent electron-rich naphthalene ring, which decreases the electrophilicity of the enone moiety. Treatment of **24** with catalytic amounts of CSA (elimination of methanol, 85% yield over 2 steps) and subsequent exposure of the resulting C-ring quinomethide/B-ring *p*-methoxyphenol to $PhI(OAc)_2$ (PIDA) gave quinomethide **25** (90% yield), whose superior electrophilicity now allowed its facile fusion with its intended nucleophilic partner. Thus, the anticipated Michael–Dieckmann reaction between highly reactive enone **25** and isoxazole **8** was achieved using a slight excess of potassium *tert*-butoxide in toluene, which afforded heptacycle **26** and its isomer 15-*epi*-**26** [91% yield, d.r. ca. 2:1 in favor of the natural C15 epimer (**26**), see below]. The relative stereochemical assignment of C4 and C4a in **26** was based on the observed $^3J_{4,4a} = 10.0$ Hz coupling constant, which is indicative of an H4,H4a *anti* relationship. From this point on, the two C15 diastereomers were carried forward as a mixture through several additional steps until separation became convenient. The use of a phenyl ester for the Michael–Dieckmann reaction was critical for success in the union of enone **25** and isoxazole **8**, in agreement with previous observations by White et al.[19] and Myers and co-workers.[4d] Indeed, the methyl ester counterpart of isoxazole fragment **8** failed to enter this cyclization, leading instead to the initially formed conjugate addition adduct whose subsequently attempted ring closure under a variety of basic conditions failed.

The next task, that of removing the Teoc group with concomitant decarboxylation, proved problematic, initially leading to decomposition[20a,b] or low yields of the desired product (i.e. **27**)[20c] under various conditions. After considerable experimentation it was found that using a freshly prepared solution of TBAF buffered with NH_4F[21] in degassed THF achieved the desired goal of removing the Teoc group in 86% yield. We hypothesized that these buffered conditions served to keep the C1,C12 β-diketone moiety of **26** in its fully protonated state, thereby allowing for smooth anion formation during the decarboxylation step. This transformation marked the successful completion of the entire carbon framework of viridicatumtoxin B (**2**).

Soon after arriving at compound **27**, we realized that its conversion into the more advanced intermediates of obligatory higher oxygenation (at C4a and C12a) would present challenges. Among the most serious issues were the multitude of functional groups present in the substrate, a problem exacerbated by the scarcity of protons around the AB ring system, which made spectroscopic analysis rather tedious, as well as the practical problems arising from the insoluble nature of the intermediates. After extensive experimentation, and as shown in Scheme 3a, the hydroxylation of **27** at C12a was finally achieved with dimethyldioxirane (DMDO) in the presence of catalytic amounts of [Ni(acac)$_2$][22] at −78 °C in dichloromethane,[23] thereby leading to the desired hydroxylated product in 50% yield after one recycle of the 40% recovered starting material. Reduction of the quinomethide moiety of the latter with NaCNBH$_3$, as a soft hydride source, was then carried out to afford naphthalene derivative **28** (+15-*epi*-**28**) in 58% combined yield for the two diastereomers (**28**/15-*epi*-**28** ca. 2:1). At this stage, the two isomers were separated chromatographically, with the natural diastereomer taken through the remaining steps. The assignment of the structural configurations of **28** and 15-*epi*-**28** were based on comparisons of the NMR spectroscopic data of the two isomers with those of the 10-methoxy counterpart **29** (Scheme 3b), whose structure had been unambiguously proven by X-ray crystallographic analysis [m.p. = 213–215 °C-(decomp) (EtOAc), see ORTEP representation, Scheme 3b].[18]

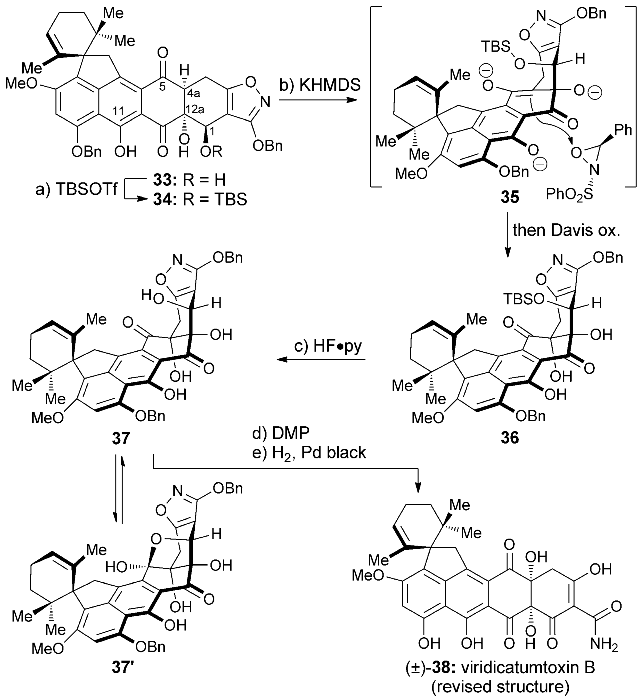


Scheme 3. **a**) Unsuccessful attempts to install the C4a hydroxy group and synthesis of C1 hydroxy compound **33** and **b**) ORTEP representation of heptacycle **29** (thermal ellipsoids at 30% probability; gray = C, red = O, blue = N, green = H). Reagents and conditions: a) [Ni(acac)$_2$] (0.2 equiv), DMDO (5.1 equiv), CH$_2$Cl$_2$, −78→−60 °C, 6.5 h, 36%, 60% brsm, 50% after one recycle; b) NaCNBH$_3$ (10 equiv), THF, −78→−60 °C, 90 min, 39% for **28**, 19% for 15-*epi*-**28**, chromatographically separated; c) 2 N aq HCl/THF 1:10, 25 °C, 5 h, quant.; d) NaBH(OAc)$_3$ (1.2 equiv), EtOAc/acetone 1:1, 40 °C, 105 min, 47%; acac = acetylacetonate, DMDO = dimethyldioxirane.

From intermediate **28**, a number of strategies and tactics were envisioned for the installment of the C4a hydroxy group (see Scheme 3a). Our initial efforts were directed at the generation of enol ether **30** and its hydroxy-directed α-epoxidation, followed by hydrolysis of the resulting epoxide to obtain compound **31**. However, all attempts to remove a molecule of methanol from ketal **28** under a variety of both Lewis and Brønsted acidic conditions did not lead to any detectable enol ether product (**30**).[24] Faced with this predicament, we proceeded to hydrolyze the dimethyl ketal moiety of **28** under acidic conditions (aq HCl, quant.) with the intention of converting the resulting triketone (**32**) into the desired product (**31**) through oxygenation of its enolate (at C4a). All attempts, however, to achieve this conversion were met with failure (see **32** to **31**, Scheme 3a). The reluctance of these substrates to react as projected may be attributed to unwanted rearrangement pathways, including β-elimination/aromatization or ring-expansion/lactone formation involving the C12a hydroxy group.[4a,25]

Speculating that a C4a,C5 diol could be introduced through dihydroxylation, we next attempted to reduce the C5 ketone within **32** (see Scheme 3a) to its corresponding alcohol by employing 1,3-directed reduction reagents[26] such as NaBH(OAc)$_3$, expecting that we might eventually be able to dehydrate the latter to the desired C4a,C5 olefinic bond within ring B. Surprisingly, however, treatment of triketone **32** with a slight excess of NaBH(OAc)$_3$ in EtOAc/acetone (1:1) at 40 °C produced the 1,2-directed reduction product **33** (47% yield) instead, as evident from diagnostic HMBC correlations. This result seemingly stands in contrast to the recently reported 1,3-reduction of a similar system by Tatsuta et al.,[27] but is most likely a result of the electron-withdrawing effect exerted by the adjacent isoxazole system which renders the C1 ketone more electrophilic. Interestingly, the use of solvents other than EtOAc/acetone (1:1) resulted in intractable mixtures of reduction products. Recognizing the potential implications of this unexpected reduction, and building on the intelligence we had accumulated thus far on the reactivity of our system, we reasoned that a substrate such as **33** could be less prone to the suspected undesired reactions such as β-elimination followed by a thermodynamically downhill aromatization of ring A.

Following this reasoning, and to exploit the fortuitous formation of **33**, the C1 hydroxy group of the latter was silylated to afford TBS ether **34** (TBSOTf, 2,6-lutidine, 61% yield, Scheme 4). Much to our delight, the desired C4a hydroxylation was successfully performed by generating the trianion (**35**) of **34** with excess KHMDS at −78 °C and quenching it with the Davis oxaziridine reagent,[28] thereby leading to C4a-hydroxylated compound **36** (20% yield



Scheme 4. C4a oxidation and completion of the synthesis. Reagents and conditions: a) TBSOTf (40 equiv), 2,6-lutidine (60 equiv), CH_2Cl_2, 0→25 °C, 1 h, 61 %; b) KHMDS (3.4 equiv), THF, −78 °C, 1 h; then Davis ox. (3.9 equiv), −78 °C, 1.7 h, 20 % + 45 % recovered **34**; c) HF·py (excess), MeCN, 0→50 °C, 25 h, 61 %; d) DMP (3.0 equiv), DCE, 0→50 °C, 7.5 h, 66 %; e) H_2, Pd black (4.9 equiv), 1,4-dioxane/MeOH 1:1, 25 °C, 8 min, 98 %; TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, KHMDS = potassium hexamethyldisilazide, Davis ox. = (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine, py = pyridine, DMP = Dess–Martin periodinane, DCE = 1,2-dichloroethane.

+ 45 % recovered starting material, 36 % brsm). Key to the success of this reaction were the free phenol at C11, an unprotected alcohol at C12a (which allows alkoxide formation, thereby preventing β-elimination), and protection of the secondary alcohol at C1. Structural deviations from this substrate resulted in no conversion, rearrangement pathways, or β-elimination of the C12a oxygen atom. The stereochemical outcome of this hydroxylation was revealed by NOESY correlations of product **36** (see the Supporting Information), and was in agreement with our expectations based on steric considerations (see structure **35**, Scheme 4).

Removal of the TBS group from compound **36** with HF·py then led to the expected hydroxy compound **37** (61 % yield). From NMR studies, we surmised that compound **37** exists in equilibrium with its cyclic hemiacetal isomer **37**′, with the two isomers interconverting slowly as evidenced from their unusually broad ^{1}H NMR signals at ambient temperature. In support of this notion was the fact that the ^{1}H NMR spectrum of this mixture acquired at −40 °C displayed two sets of signals. Finally, oxidation of **37**/**37**′ with DMP[29] furnished the corresponding C1 ketone (66 % yield), which was subjected to hydrogenolysis[4d] (two benzyl ethers and an N−O bond; H_2, Pd black, 98 % yield) to afford compound (±)-**38** as shown in Scheme 4. The physical properties of (±)-**38** matched those reported for viridicatumtoxin B[7] except for the presence of the C5 signal at $\delta = 194.1$ ppm in the ^{13}C NMR spectrum of (±)-**38** and the absence of the reported[7] C5 signal at $\delta = 116.4$ ppm.[30] No spectroscopic evidence for the existence of an epoxy hemiacetal structural motif was observed in the ^{13}C NMR spectrum of (±)-**38**, thus compelling us to revise the structure of natural viridicatumtoxin B to that of **38**. Pleasantly, synthetic viridicatumtoxin B (**38**) crystallized in crystals suitable for X-ray analysis from CH_2Cl_2/EtOH [m.p. = 245–247 °C(decomp), see ORTEP representation, Figure 3], which provided unambiguous proof of its structure.[18]

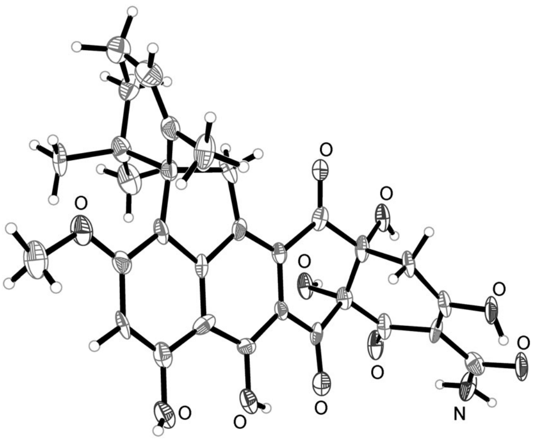


Figure 3. ORTEP representation of synthetic viridicatumtoxin B (**38**; thermal ellipsoids at 30 % probability; gray = C, red = O, blue = N, green = H).

In conclusion, the total synthesis of racemic viridicatumtoxin B has been achieved through a highly convergent synthetic strategy from four easily accessible building blocks. This accomplishment led to the revision of the originally assigned epoxy hemiacetal structure of viridicatumtoxin B (**2**, Figure 1) to its hydroxy ketone form (**38**, Scheme 4). Efforts currently in progress aim to achieve an enantioselective total synthesis of viridicatumtoxin B (**38**) and confirm its absolute configuration. The developed chemistry sets the stage for further advances to occur in the field, including the design, synthesis, and biological evaluation of analogues of the viridicatumtoxins as potential leads for drug discovery to combat bacterial infections.

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