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REVIEW ARTICLE

Synthetic studies of viridiofungins, broad-spectrum antifungal agents and serine palmitoyl transferase inhibitors

Naoya Kumagai and Masakatsu Shibasaki

Viridiofungins are alkyl citrate natural products characterized by their inhibitory effects on squalene synthase and serine palmitoyl transferase. Their activities as broad-spectrum antifungal agents as well as blocking agents for the biosynthesis of sphingolipids have inspired the development of several approaches toward their stereoselective total synthesis. Structurally, these natural products are a family of hybrid molecules comprising a longer alkyl chain and a citric acid unit, rendering an asymmetric structure that is difficult to access. Herein, we summarize the synthetic approaches to this attractive class of natural products, including proficient synthetic strategies for constructing the densely and chirally functionalized citric acid unit with high polarity. Particular emphasis is placed on methods for furnishing stereogenic centers in the highly constrained carbon framework.
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INTRODUCTION

In 1993, viridiofungins A, B and C were isolated from a strain of *Trichoderma viridae* Pers. (Fungi, Hyphomycetes) and are considered a novel family of squalene synthases, which are of interest as antifungal agents as well as cholesterol-lowering therapeutics (Figure 1).[1] They are categorized as alkyl citrate natural products, a family of naturally occurring squalene synthase inhibitors including zaragozic acids,[2,3] and possess a different aromatic α-amino acid unit: Tyr, Phe and Trp for viridiofungin A, B and C, respectively. Six additional derivatives, $A_{1–4}$, B_2 and Z_2, were later disclosed as analogs that differ in the minor structure of the alkyl chain (oxidation level at C-13, or chain length) or lack the α-amino acid unit.[4] The characteristic feature of viridiofungins that makes them unique in the alkyl citrate family is their inhibitory activity toward serine palmitoyl transferase, which is involved in the first step of sphingolipid biosynthesis at nanomolar concentrations.[4–6] As sphingolipids are the major components of the lipid raft, where non-structural viral proteins of hepatitis C virus accumulate, the inhibitory effect of serine palmitoyl transferase offers a therapeutic option for the treatment of hepatitis C virus infection.[7] Given these attractive biological activities, several synthetic routes of viridiofungins have been documented to date.[6,8] The introduction of an alkyl chain to a methylene group of the citric acid renders it chiral, significantly increasing the structural and synthetic complexity. The stereoselective construction of the densely functionalized polar citric acid unit of the molecule is perplexing, and the synthetic strategy for this part dictates the overall synthetic efficiency. In this review article, synthetic methodologies of viridiofungin derivatives are highlighted, with particular emphasis on the efficiency of the requisite stereochemical control.

SYNTHESIS VIA CATALYTIC ASYMMETRIC EPOXIDATION

In 1998, Hatakeyama and colleagues[9] reported the first total synthesis of viridiofungin. This work was particularly noteworthy because of the manifestation of four stereoisomers of viridiofungin A trimethyl ester, allowing for determination of the absolute configuration of natural viridiofungin A isolated in 1993 (Figure 2).[1] The key methodology used to introduce the requisite stereogenic center was Katsuki–Sharpless catalytic asymmetric epoxidation of trisubstituted allylic alcohol **1**, delivering enantioenriched epoxide **2** in 92% yield and 88% ee.[10–12] The synthesis commenced with *O*-protection and 1-C homologation with paraformaldehyde of 3-butyn-1-ol **3** to give **4**, whose propargylic alcohol unit was reduced by Red-Al, and subsequent treatment of the intermediate with iodine produced the desired *Z*-configured iodoalkene.[13] After protection of the primary alcohol as a tetrahydropyranyl ether, the addition of lithiated **5** to CO_2, followed by treatment with methyl iodide gave methyl ester **6**. The ester was reduced by diisobutylaluminum hydride to a primary alcohol that was protected as a *p*-methoxybenzyl (PMB) ether, and a tetrahydropyranyl-protecting group on the opposite side was removed by methanolysis using pyridinium *p*-toluene sulfonate for the subsequent key reaction, catalytic asymmetric epoxidation. The trisubstituted epoxide **2** was regioselectively opened by vinylmagnesium bromide **7** and CuI with participation of the neighboring-free hydroxyl group, thereby affording diol **8**.[14,15] The free alcohols were masked as acetonide with 2,2-dimethoxypropane under acidic

Laboratory of Synthetic Organic Chemistry, Institute of Microbial Chemistry (BIKAKEN), Tokyo, Japan
Correspondence: Dr M Shibasaki, Laboratory or Dr Naoya Kumagai of Synthetic Organic Chemistry, Institute of Microbial Chemistry (BIKAKEN), 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan.
E-mail: mshibasa@bikaken.or.jp or nkumagai@bikaken.or.jp
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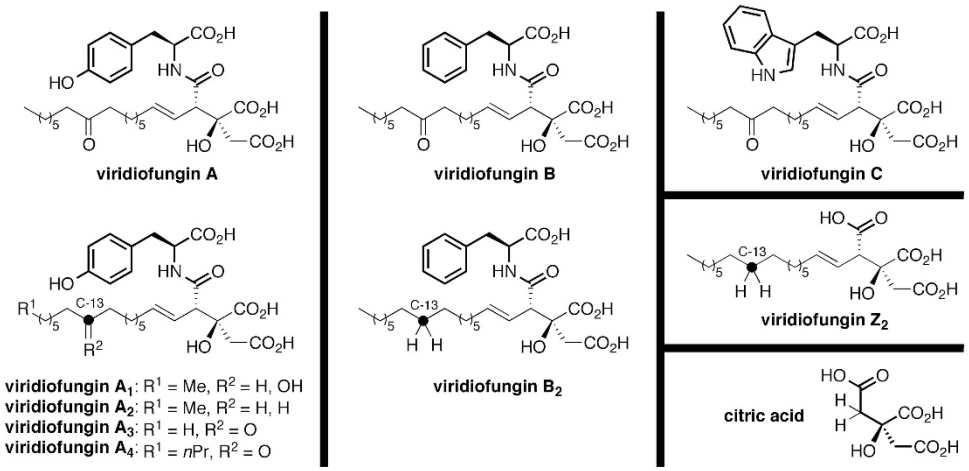

Figure 1 Structure of viridiofungin derivatives and citric acid.

conditions, and subsequent sequential oxidation with OsO_4 and $NaIO_4$ converted the terminal olefin to an aldehyde as a reactive handle for introducing an alkyl chain. Wittig reaction of aldehyde **9** and phosphonium salt **10** mediated by *n*-butyllithium connected them with the *Z*-configured double bond, and removal of two PMB groups followed by protection with *tert*-butyldimethylsilyl (TBDPS) chloride provided mono-TBDPS ether **11**. The free primary alcohol moiety of **11** was oxidized to a carboxylic acid by sequential oxidation reactions, and subsequent treatment with diazomethane afforded methyl ester **12**. Deprotection/oxidation of TBDPS ether was achieved in the four steps, including hydrolytic cleavage of the acetonide, fluoride-mediated deprotection of the TBDPS ether, Jones oxidation of the primary alcohol and methyl ester formation with diazomethane.[16] While the Jones oxidation preferentially proceeded at the less hindered primary alcohol to give **13** after lactonization, an undesired oxidation was also occurring, as evidenced by the formation of **14**. Photoirradiation of **13** in the presence of PhSSPh allowed for olefin isomerization to give the *E*/*Z* = 82/18 mixture, which was purified to give geometrically pure (*E*)-**15** by preparative TLC. Chemoselective hydrolysis of the lactone moiety of **15** followed by diazomethane/Jones oxidation gave carboxylic acid **16**.[16] To determine the absolute configuration of viridiofungin, **16** was subjected to amidation with both H-Tyr-OMe and H-D-Tyr-OMe using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) hydrochloride,[17] furnishing trimethyl esters of viridiofungin A and *epi*-1-viridiofungin A. This synthetic scheme is well designed and a slight modification of the reaction sequence enabled access to *epi*-**9** from intermediate **8** via **17**. Identical reaction sequences were applied to *epi*-**9** to produce two other stereoisomeric trimethyl esters, *epi*-2-viridiofungin A and *epi*-3-viridiofungin A. Comparison of the optical rotations and ^1H and ^{13}C NMR spectra of these four stereoisomers with the trimethyl ester derived from natural viridiofungin A ($[\alpha]_D^{25}$ −23.3°) indicated that viridiofungin A has a (3*S*,4*S*,2′*S*) configuration (synthetic: $[\alpha]_D^{26}$ −19.1°).

The labile nature of viridiofungin A under basic conditions hampered the hydrolysis of trimethyl ester to furnish viridiofungin A. This fact prompted the team led by Hatakeyama to devise a new synthetic route with various improvements (Figure 3).[18] The revised synthesis began with the identical starting material, 3-butyn-1-ol **3**, which gave structurally different trisubstituted allylic alcohol **18** for a Katsuki–Sharpless catalytic asymmetric epoxidation after six transformation steps.[10–12] Once the enantioenriched (87% ee) epoxide **19** was obtained, a subsequent three-step sequence converted the primary alcohol unit to a *tert*-butyl ester-to allow for global deprotection under acidic conditions at the final stage. The tetrahydropyranyl ether was hydrolyzed to the hydroxyl group for a directed epoxide opening that proceeded similarly to the previous synthesis.[14,15] The thus-formed diol was protected as a cyclic carbonate by triphosgene, and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone removed the PMB group to give primary alcohol **21**. Jones oxidation[16] followed by treatment with *O*-*tert*-butyl-*N*,*N*′-diisopropylisourea[19] gave precursor **22** for olefin cross metathesis to install an alkyl chain with terminal olefin **23**.[20] Grubbs second-generation catalyst **24**[21] linked them with *E*/*Z* = 88/12 in a reasonable yield (65%), and subsequent hydrolysis of the cyclic carbonate was fulfilled in a sequential manner; opening with allylic alcohol and palladium-catalysed reductive deallylation.[22] The exposed primary alcohol unit of **25** was oxidized to a carboxylic acid and amide bond formation was achieved with H-Tyr-O*t*Bu using EDCI hydrochloride,[17] *N*-methylmorpholine, and 1-hydroxybenzotriazole. Global deprotection of the three *tert*-butyl esters readily proceeded with formic acid to furnish the tricarboxylic acid, which constitutes the first demonstration of the total synthesis of viridiofungin A.

SYNTHESIS VIA CATALYTIC ASYMMETRIC HYDROGENATION

Ghosh *et al.* reported a different approach utilizing a Mukaiyama aldol reaction[23–25] to construct the densely functionalized polar part of viridiofungin A.[26] Dihydrofuran **28** was used as an optically active nucleophile prepared from γ-ketoester **26**, involving Corey–Bakshi–Shibata reduction[27] using oxazaborolidine catalyst **27** (Figure 4).[28–30] The aldol reaction of **28** with engineered α-ketoester **29** mediated by $TiCl_4$ presumably proceeded through oxonium cation intermediate **30** with minimum steric constraint, which was *in situ* reduced by Et_3SiH to give **31** with a fully saturated tetrahydrofuran ring. An efficient chirality transfer from **28** was manifested, as evidenced by the high diastereomeric ratio of **31** (>20/1). A hydroboration/oxidation sequence converted the triple bond of **31** to the corresponding carboxylic acid, the ethyl ester moiety was hydrolyzed by LiOH, and treatment of the resulting dicarboxylic acid with *O*-*tert*-butyl-*N*,*N*′-diisopropylisourea[19] delivered di-*tert*-butyl ester **32**. Exposure of **32** to $Cu(OTf)_2$ (20 mol%) in the presence of Ac_2O in refluxing toluene led to tetrahydrofuran ring opening and *O*-acetylation, together with unexpected deprotection/cyclization of the di-*tert*-butyl esters to give

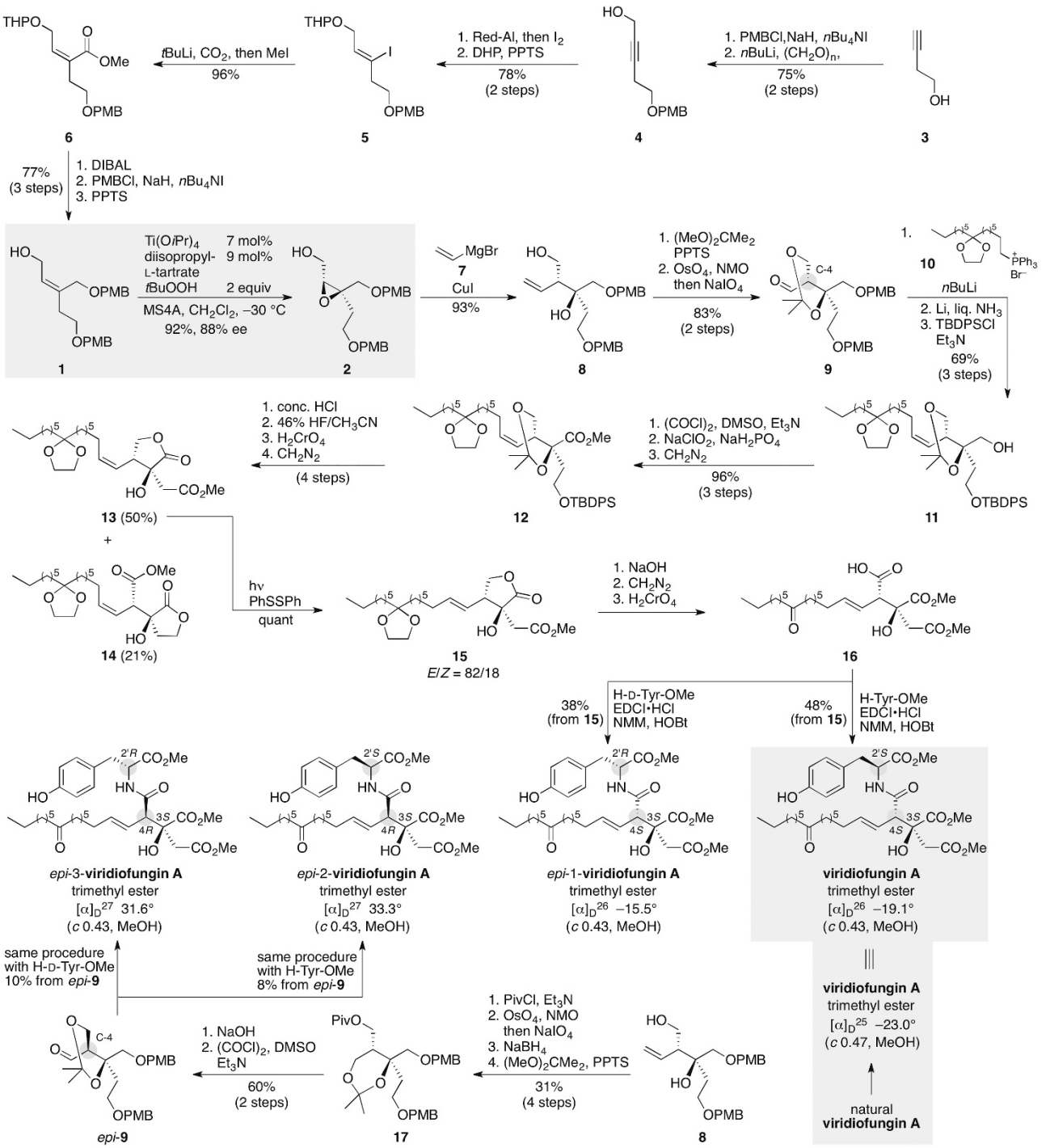

Figure 2 First total synthesis of viridiofungin A trimethyl ester and determination of its absolute configuration. DHP, 3,4-dihydro-2*H*-pyran; DIBAL, diisobutylaluminum hydride; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt, 1-hydroxybenzotriazole; MS4A, molecular sieves 4 Å; NMO, *N*-methylmorpholine *N*-oxide; NMM, *N*-methylmorpholine; PMB, *p*-methoxybenzyl; PPTS, pyridinium *p*-toluenesulfonate; TBDPS, *tert*-butyldiphenylsilyl.

anhydride **33**. After regenerating di-*tert*-butyl ester **34** by sequential treatment with aqueous acetic acid and *O*-*tert*-butyl-*N*,*N*′-diisopropylisourea,[19] two acetyl groups were removed by (allyl)MgBr and the resulting alcohols were protected as silyl ethers. The thus-obtained **35** was oxidized by ozone to generate the aldehyde requisite for subsequent Julia–Kocieński olefination with sulfonyltetrazole **36**,[31] which was originally used in Hiersemann's synthesis in 2004 (*vide infra*).[32] The desired coupled product **37** was obtained exclusively in the *E*-configuration, followed by deprotection of the silyl ethers and Jones oxidation to afford **38**.[16] Amide formation with H-Tyr-O*t*Bu and deprotection of three *tert*-butyl esters according to Hatakeyama's second-generation procedure[18] delivered viridiofungin A.

SYNTHESIS VIA CATALYTIC ASYMMETRIC ALDOL REACTION

In contrast to the two above-discussed synthetic examples, where catalytic asymmetric carbon–oxygen bond or carbon–hydrogen bond

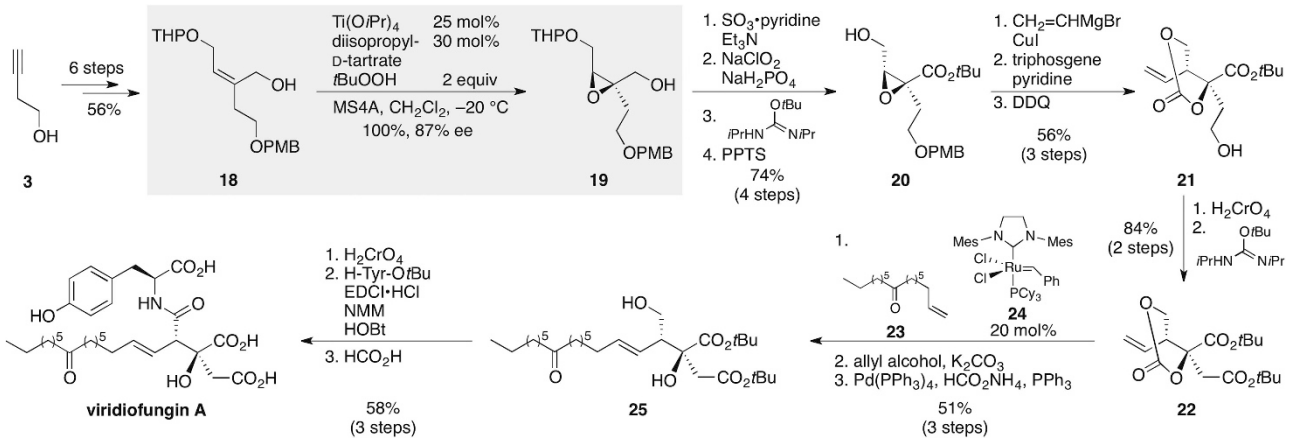

Figure 3 Revisited synthesis of viridiofungin A by Hatakeyama *et al.* DDQ, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; EDCI, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; HOBt, 1-hydroxybenzotriazole; NMM, *N*-methylmorpholine; PPTS, pyridinium *p*-toluenesulfonate.

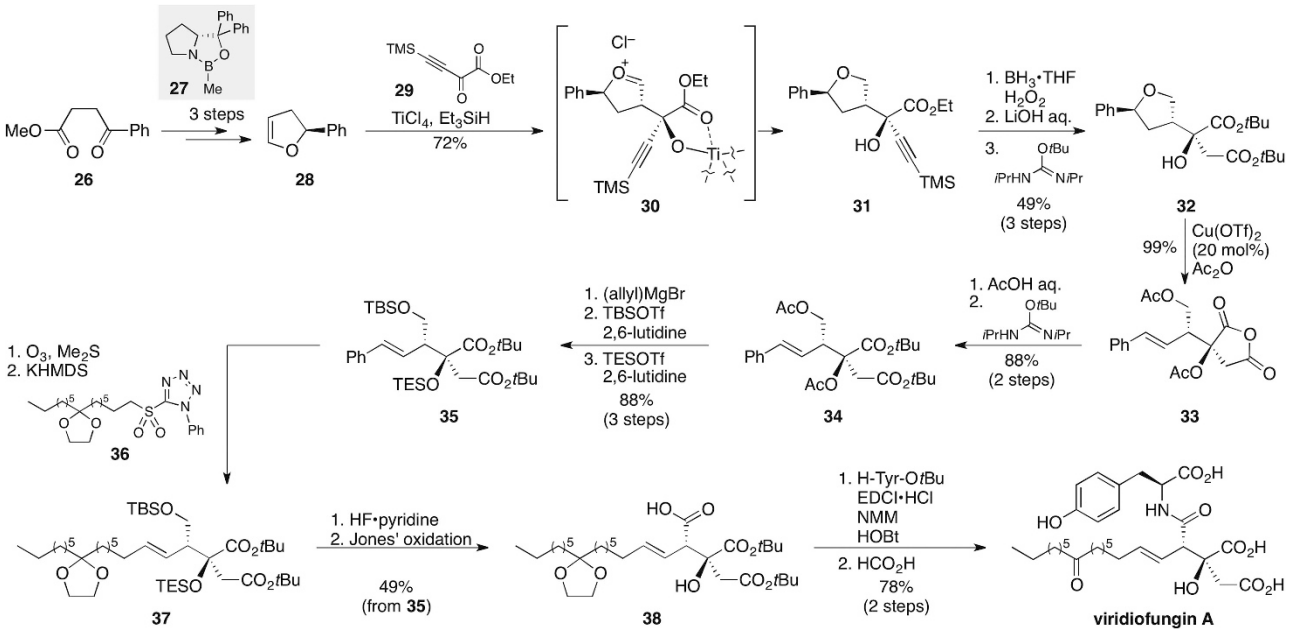

Figure 4 Total synthesis of viridiofungin A by Ghosh *et al.* EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt, 1-hydroxybenzotriazole; KHMDS, potassium hexamethyldisilazide; NMM, *N*-methylmorpholine; TBS, *tert*-butyldimethylsilyl; TES, triethylsilyl.

formations were exploited, the total synthesis reported by Shibasaki *et al.* utilizes a catalytic asymmetric carbon–carbon bond-forming reaction to enable the construction of the requisite carbon framework and introduction of the chirality in a single step (Figure 5).[33] To construct the tetrasubstituted stereogenic center of viridiofungin A, α-sulfanyl lactone **40** was designed as a soft Lewis basic pronucleophile, and subjected to a direct catalytic asymmetric aldol reaction with PMB-protected glycoaldehyde **39** promoted by a soft Lewis acid ($AgPF_6$/ligand **41**)/Brønsted base (1,8-diazabicyclo [4.3.0]undec-7-ene) cooperative catalyst. The reaction efficiently proceeded with 3 mol% of catalyst loading and the desired *syn*-configured aldol product **42** was obtained over 20 g with high enantioselectivity (98% ee). The lactone was reduced with $LiAlH_4$ and the resulting two primary hydroxyl groups were protected by TBDPS groups to give **43**. The carbon–sulfur bond of **43** was replaced with a carbon–oxygen bond with inversion of the configuration by *S*-methylation with MeOTf, followed by intramolecular epoxide formation with the neighboring secondary hydroxyl group. After removing the PMB group with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, hydroxyl group-directed epoxide opening using vinyl cuprate derived from **45** gave a diol,[14,15] which was protected as an acetonide, and deprotection of TBDPS groups delivered bis primary alcohol **46**. Sequential treatment of **46** with oxidation then *tert*-butyl ester formation using *O-tert*-butyl-*N*,*N*′-diisopropylisourea[19] gave rise to the previously known intermediate **25**.[18] After oxidation of the primary alcohol of **25** by CrO_3,[16] H-Tyr-O*t*Bu and *O*-1-(2-butyn)-ylated H-Tyr-O*t*Bu **47** were coupled using (7-azabenzotriaol-1-yl)-1, 1,3,3-tetramethyluronium hexafluorophosphate as an amide-coupling reagent,[17] in order to access viridiofungin A and NA808, respectively. NA808 is a druggable analog of viridiofungin A that is anticipated to block the proliferation of hepatitis C virus by inhibiting sphingolipid biosynthesis.[34,35]

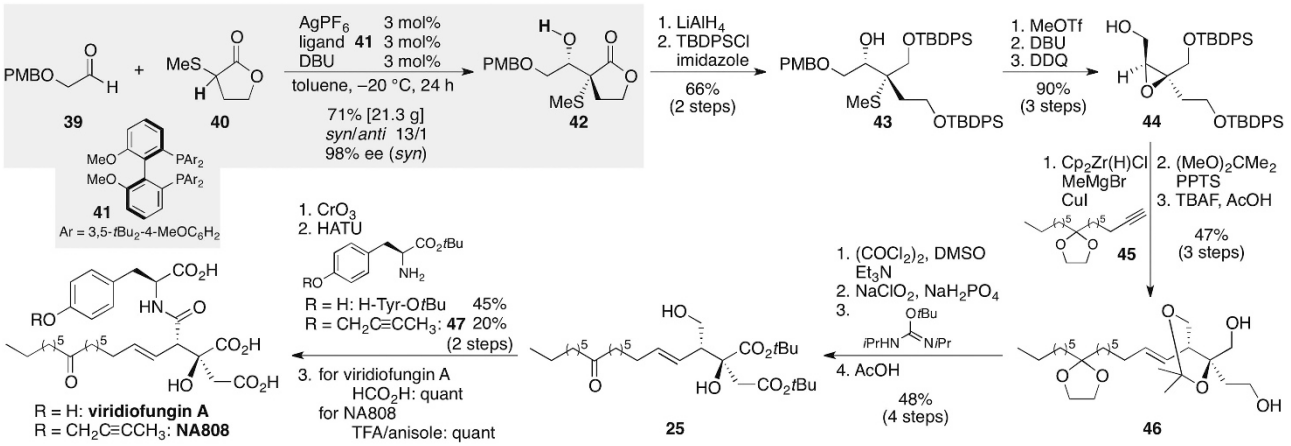

Figure 5 Total synthesis of viridiofungin A and NA808 by Shibasaki *et al*. DBU, 1,8-diazabicyclo[4.3.0]undec-7-ene; DDQ, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; DMSO, dimethylsulfoxide; HATU, (7-azabenzotriaol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; PPTS, pyridinium *p*-toluenesulfonate; TBAF, tetrabutylammonium fluoride; TFA, trifluoroacetic acid.

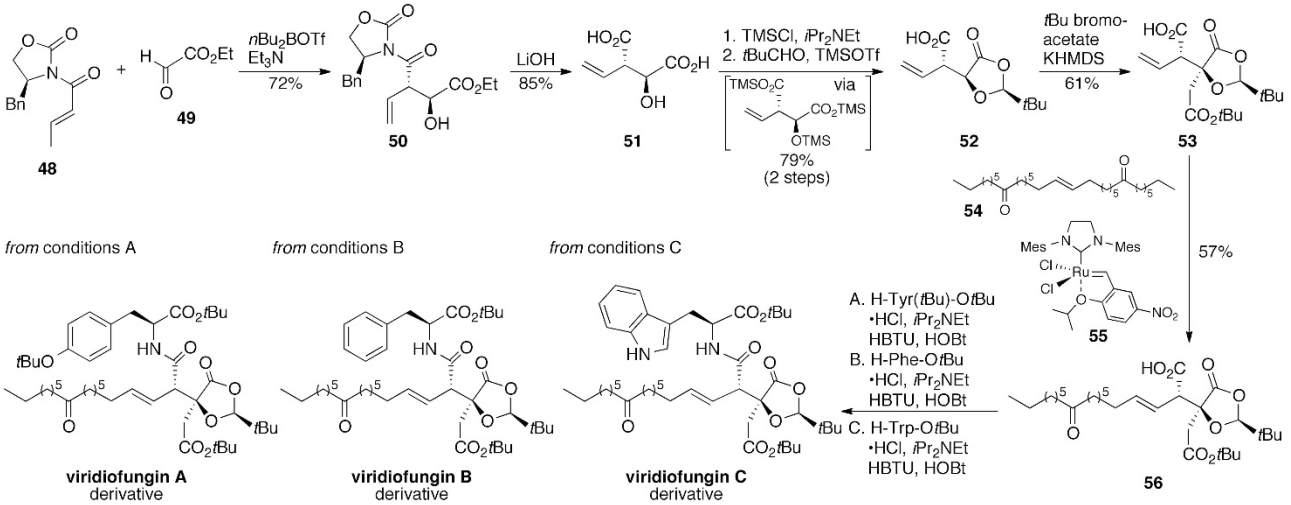

Figure 6 Total synthesis of derivatives of viridiofungin A–C by Barrett *et al.* HBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; KHMDS, potassium hexamethyldisilazide; TMS, trimethylsilyl.

SYNTHESIS VIA CHIRAL AUXILIARY

The use of a chiral auxiliary for the synthesis of optically active compounds can be categorized as a classical synthetic methodology. Compared with asymmetric catalysis, the mandatory use of a stoichiometric chiral source can be a drawback, but reliable stereoselectivity as well as robustness and a broad scope of reactions make auxiliary-based approaches applicable for a myriad of practical syntheses. In particular, when inexpensive materials in the chiral pool are used as auxiliaries, at least the cost for chiral information is minimized despite being a low atom-economic process. Oxazolidinone-based chiral auxiliaries developed by Evans are representatives of such auxiliaries, readily prepared from inexpensive α-amino acids.[36] The concise total synthesis of viridiofungin A–C derivatives reported by Barrett *et al.*[37] explicitly demonstrates the usefulness of the chiral auxiliary approach in target-oriented synthesis (Figure 6). The synthesis began with a boron-mediated aldol reaction of oxazolidinone **48**,[19,38] prepared from inexpensive L-phenylalanine and ethyl glyoxylate **49**, affording adduct **50** with the desired vicinal stereochemistry at newly formed stereogenic centers. The oxazolidinone auxiliary and the ethyl ester were readily hydrolyzed by LiOH to give diacid **51**, which was converted to acetal **52** with pivaldehyde and trimethylsilyl trifluoromethanesulfonate via a tris-trimethylsilylated intermediate.[39] Introduction of the requisite acetate unit with the correct stereochemistry was achieved by following the strategy of self-reproduction of stereochemistry developed by Seebach;[40] deprotonation of **52** with lithium hexamethyldisilazide and subsequent addition to *tert*-butyl bromoacetate delivered **53**, a precursor of the cross metathesis reaction to install the long alkyl chain unit. The use of terminal alkene **23** with Grubbs second-generation catalyst **24** (Figure 3)[20,21] proved unsuccessful in the specific case of **53**, and only homodimerization of **24**–**54** occurred. Careful experimentation identified that cross metathesis with dimer **54** using 20 mol% of Grela catalyst **55** gave the desired product **56** in moderate yield.[41] With the readily cleavable five-membered acetal, viridiofungin A–C derivatives were synthesized from **56** with the corresponding amino acid *tert*-butyl esters using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate as an amide-coupling reagent.[17]

SYNTHESIS VIA HPLC SEPARATION OF STEREOISOMERS

Hiersemann *et al.*[32,42] reported a different approach to viridiofungin A triesters using [2,3]-Wittig rearrangements to construct the tertiary alcohol at the polar citric acid unit (Figure 7). Anticipating the

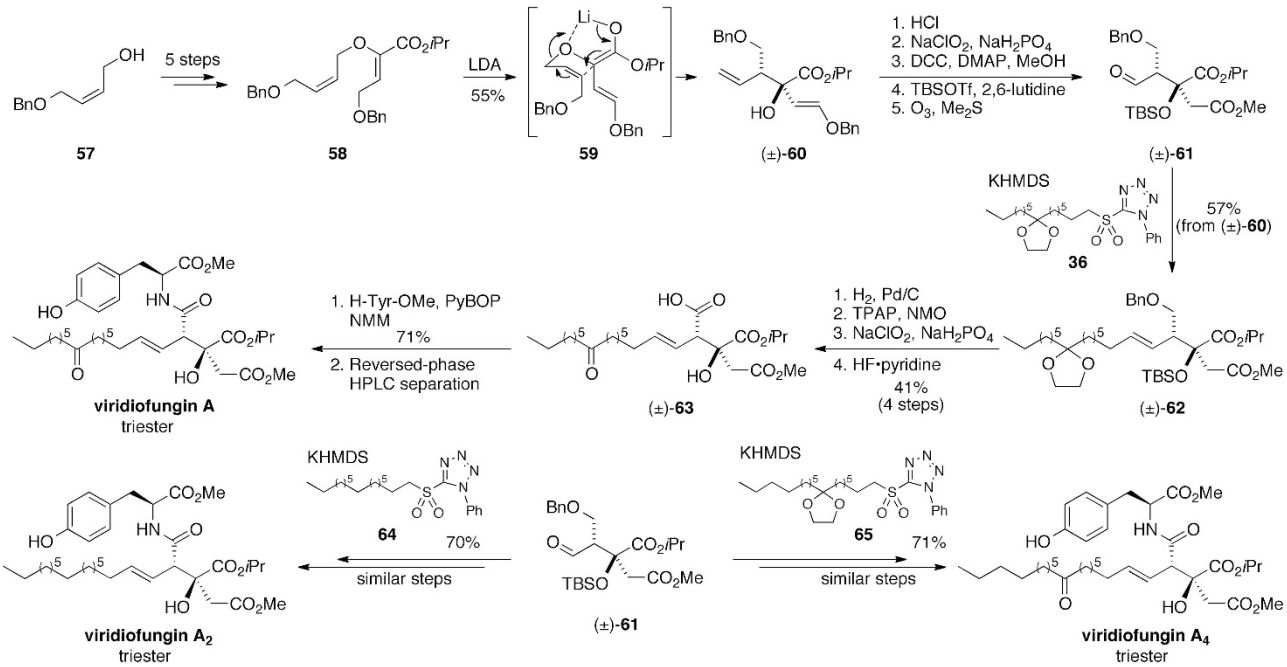

Figure 7 Total synthesis of derivatives of viridiofungin A triesters by Hiersemann *et al.* DCC, dicyclohexylcarbodiimide; DMAP, *N,N*-dimethylaminopyridine; HPLC, high-performance liquid chromatography; KHMDS, potassium hexamethyldisilazide; LDA, lithium *N,N*-diisopropylamide; NMM, *N*-methylmorpholine; PyBOP, 1*H*-benzotriazol-1-yloxy-tri(pylimidino)phosphonium hexafluorophosphate; TBS, *tert*-butyldimethylsilyl; TPAP, tetrapropylammonium perruthenate.

coupling with optically pure amino acid at the last stage, the synthesis was promoted by racemic intermediates and isolation of the stereoisomers of viridiofungin A triesters relied on reversed-phase HPLC separation at the final stage. Although the overall efficiency of accessing molecules with the correct stereochemistry was diminished, a highly flexible synthetic route could be applied, offering the opportunity to provide unnatural stereoisomers for prospective biological studies. Allyl vinyl ether **58** as a precursor of the [2,3]-Wittig rearrangement was prepared from **57** in a five-step sequence.[43] Enolate formation by lithium *N,N*-diisopropylamide-induced sigmatropic rearrangements as delineated in **59** to give tertiary alcohol (±)-**60** in a racemic form, possessing the requisite functionalities for viridiofungins in the correct relative stereochemistry. The enol ether moiety was hydrolyzed to aldehyde, and subjected to oxidation/esterification using methanol, dicyclohexylcarbodiimide, and 4-(dimethylamino)pyridine to afford the methyl ester. For installation of the alkyl chain by the Julia–Kocieński reaction,[31] the tertiary alcohol was protected due to the TBS ether and terminal olefin oxidizing to aldehyde by ozone. The thus-formed (±)-**61** was coupled with sulfonyltetrazole **36** using potassium hexamethyldisilazide, affording (±)-(*E*)-**62** as a single geometric isomer. Hydrogenolysis of the benzyl ether, followed by sequential oxidation reactions using tetrapropylammonium perruthenate[44]/*N*-methylmorpholine oxide and $NaClO_2/NaH_2PO_4$, and subsequent removal of the TBS group furnished carboxylic acid (±)-**63** for final coupling with H-Tyr-OMe. Amide formation was performed with 1*H*-benzotriazol-1-yloxy-tri(pylimidino)phosphonium hexafluorophosphate (PyBOP) and *N*-methylmorpholine to deliver a mixture of stereoisomers of viridiofungin A triester, which were isolated by reversed-phase HPLC.[17] With aldehyde (±)-**61**, a Julia–Kocieński reaction using sulfonyltetrazoles without ketone functionality (**64**) or with additional 2-methylene groups (**65**) furnished intermediates corresponding to triesters of viridiofungin A_2 and A_4 that were accessed by applying similar reaction sequences.

CONCLUSION

Stereoselective syntheses of viridiofungins developed by five independent research groups were reviewed. As the densely functionalized polar citric acid unit is a characteristic feature of these alkyl citrate natural products, each group used a different approach to construct the carbon framework and stereogenic centers of the unit. The first three examples exploited asymmetric catalysis amenable to obtaining enantioenriched intermediates with minimal use of generally expensive and less available chiral sources. The latter two groups used a stoichiometric amount of the chiral source or HPLC separation. Although synthesis via asymmetric catalysis appears ideal in one respect, the reaction conditions pose severe limitations on the substrate scope and the operation requires strict control. The advantage of the chiral auxiliary approach is the broad scope of reaction types and substrate sets, allowing for selection of the most suitable starting material to streamline the following synthetic pathways. Indeed, the auxiliary approach presented above accomplished the synthesis in an appreciably small number of steps. These synthetic routes should be evaluated by assessing the overall efficiency and availability of reagents and catalysts, ease of the purification processes, as well as the number of steps. The attractive biological activity of vidridiofungins and their derivatives makes these alkyl citrate natural products desirable targets for the development of artful synthetic strategies, with the potential for higher efficiency and elegance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DEDICATION

This article is dedicated to Professor Hamao Umezawa for his achievements in science and medicine.

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