

Total synthesis of viridifungin A†

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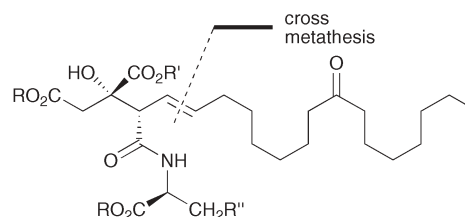
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Viridifungin A, a member of amino alkyl citrate antibiotics from *Trichoderma viride*, was enantioselectively synthesized in naturally occurring form for the first time, employing regio- and stereoselective opening of the chiral glycidate with vinylmagnesium bromide and alkene cross metathesis of the citric acid core and hexadec-15-en-8-one as key steps.

Viridifungin A (**1**) was isolated from a strain of *Trichoderma viride* Pers., together with viridifungin B and C, by Harris *et al.*¹ The viridifungins have potent, broad spectrum antifungal activity which arises from the nanomolar level of inhibition of serine palmitoyltransferase.² These compounds were also found to inhibit Ras farnesyl transferase³ as well as squalene synthase⁴ *in vitro* at the micromolar level. The viridifungins have interesting structures consisting of a common citric acid moiety having a C-16 long chain and an aromatic amino acid residue such as tyrosine, phenylalanine, and tryptophan.¹ The absolute structure of viridifungin A (**1**) was determined by our enantiocontrolled synthesis of viridifungin A trimethyl ester (**2**).⁵ However, we could not achieve the synthesis of viridifungin A (**1**) from trimethyl ester **2** because saponification of **2** caused decomposition, possibly *via* a retro-aldol process. Recently, Hiersemann *et al.*⁶ reported an efficient synthesis of viridifungin A triester (**3**) based on ester dienolate [2,3]-Wittig rearrangement; however, they have not synthesized viridifungin A (**1**). We describe herein the first total synthesis of viridifungin A (**1**).

Taking into account the labile nature of **1** under basic conditions, we selected tri-*tert*-butyl ester **4** as a precursor with anticipation of its successful deprotection under mild acidic conditions in the final step of the synthesis. To access **4**, we envisaged the strategy which relies on alkene cross metathesis⁷ between the citric acid core **5** and hexadec-15-en-8-one (**6**) as indicated in Fig. 1.

Our synthesis began with the stereoselective six-step preparation of *Z*-allylic alcohol **7** from 3-butyne-1-ol according to our previously established procedure (Scheme 1).⁵ Katsuki–Sharpless asymmetric epoxidation⁸ of **7** afforded epoxide **8** in 87% ee.⁹ Successive Parikh–Doering oxidation,¹⁰ NaClO₂ oxidation,¹¹ esterification using *N,N'*-diisopropyl-*O*-2-*tert*-butylisourea,¹² and removal of the THP protecting group converted **8** into glycidate **9** in good yield. Upon exposure of **9** to vinylmagnesium bromide in the presence of CuI, highly regio- and stereoselective nucleophilic opening of the epoxide occurred to give diol **10** exclusively. After protection of **10** as its cyclic carbonate,¹³ removal of the *p*-methoxybenzyl protecting group afforded **11** which was then



viridifungin A

- 1**: R = R' = H, R'' = *p*-(OH)-Ph
2: R = R' = Me, R'' = *p*-(OH)-Ph
3: R = Me, R' = ^tPr, R'' = *p*-(OH)-Ph
4: R = R' = ^tBu, R'' = *p*-(OH)-Ph

viridifungin B: R = H, R' = Ph
 viridifungin C: R = H, R' = β -indolyl

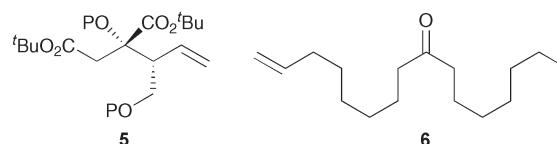
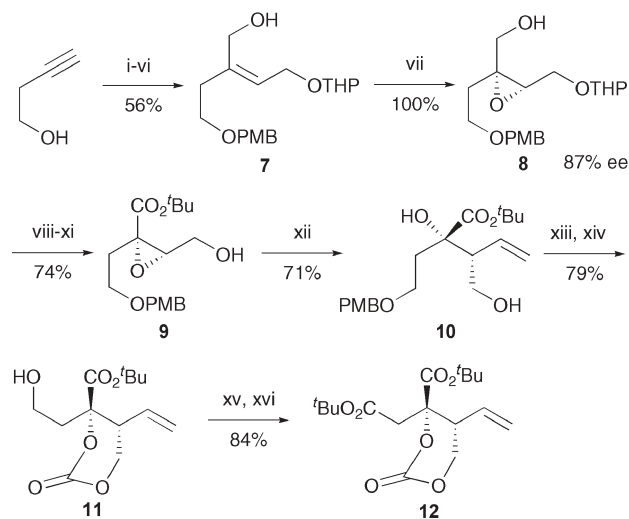


Fig. 1



Scheme 1 Reagents and conditions: (i) *p*-(MeO)C₆H₄CH₂Cl, NaH, ^tBu₄NI, THF; (ii) ^tBuLi, (CH₂O)_n, THF; (iii) Red-Al, Et₂O, 0 to 25 °C, then I₂, -50 to 25 °C; (iv) PPTS, DHP, CH₂Cl₂; (v) ^tBuLi, CO₂, Et₂O, -78 °C, then MeI, DMF; (vi) DIBAH, CH₂Cl₂, -78 °C; (vii) diethyl D-tartrate (0.3 eq.), Ti(OⁱPr)₄ (0.25 eq.), ^tBuOOH (2 eq.), molecular sieves, CH₂Cl₂, -20 °C; (viii) SO₃·pyridine, Et₃N, DMSO, CH₂Cl₂; (ix) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, ^tBuOH–H₂O (4:1); (x) *N,N'*-diisopropyl-*O*-2-*tert*-butylisourea, CH₂Cl₂; (xi) PPTS, MeOH; (xii) CH₂=CHMgBr (10 eq.), CuI (1 eq.), THF, -26 °C; (xiii) triphosgene, pyridine, THF; (xiv) DDQ, CH₂Cl₂–H₂O (20:1); (xv) H₂CrO₄, aq. acetone, -10 °C; (xvi) *N,N'*-diisopropyl-*O*-2-*tert*-butylisourea, CH₂Cl₂.

† Electronic supplementary information (ESI) available: experimental details. See <http://www.rsc.org/suppdata/cc/b5/b500660k/>
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Table 1 Alkene cross metathesis of **12** with hexadec-15-en-8-one (**6**)^a

Reaction scheme showing the cross metathesis of **12** and **6** using catalysts **13** or **14** to produce **15** and its Z-isomer.

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield	
					15 + Z-isomer (%) ^b [E:Z] ^c	12 (%)
1	13	CH ₂ Cl ₂	40	84	65 (86) [88:12]	24
2	13	Toluene	100	72	33 (65) [70:30]	49
3	14	CH ₂ Cl ₂	40	16	48 (100) [85:15]	52
4	14	Toluene	100	72	57 (66) [89:11]	14

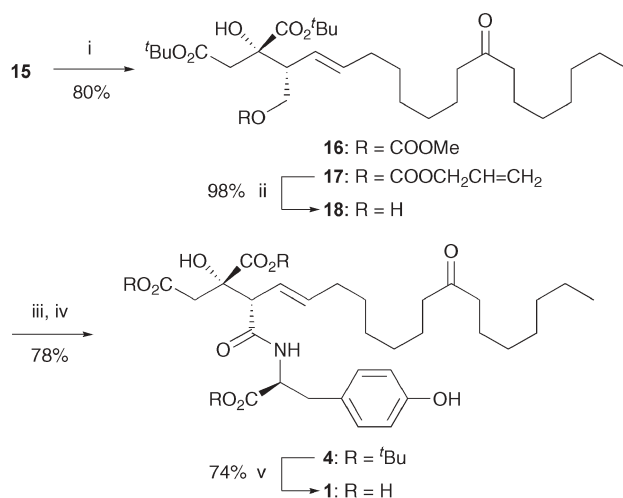
^a All reactions were carried out using **12** (1 eq.), **13** or **14** (0.2 eq.) and **6** (2 eq.). ^b The yields in the parentheses were calculated based on recovered **12**. ^c Determined by ¹H NMR analysis.

subjected to Jones oxidation followed by *tert*-butyl esterification to give diester **12**.

The crucial alkene cross metathesis of **12** with hexadec-15-en-8-one (**6**)¹⁴ was then examined under various conditions using ruthenium carbene complexes.¹⁵ Although Grubbs' first generation catalyst¹⁶ gave unsuccessful results, it was gratifyingly found that Grubbs' second generation catalyst **13**¹⁷ and Hoveyda's catalyst **14**¹⁸ effectively promoted the desired cross metathesis reaction (Table 1). Thus, upon reaction of **12** with 2 equivalents of **6** in the presence of 20 mol% of **13** in boiling CH₂Cl₂ for 3.5 days, **15** and its *Z*-isomer were obtained in a ratio of 88:12 in 65% yield, together with unreacted **12** (24%) (entry 1). When this reaction was conducted using **14** with a shorter reaction time, both the *E/Z*-ratio and the total yield became lower [*E:Z* = 85:15 (48%)] although unreacted **12** was recovered without loss (entry 3). It was observed that catalyst **14** is more effective than catalyst **13** at higher temperature although both reactions were accompanied by appreciable decomposition (entries 2 and 4).

Having constructed the required carbon skeleton as **15**, we then investigated its conversion into viridifungin A (**1**). Methanolysis of **15** in the presence of K₂CO₃ at -20 °C initially gave carbonate **16** but the prolonged reaction time caused decomposition of **16** rather than producing the desired diol **18**. However, this result allowed us to come up with the following transformations for the preparation of **18** (Scheme 2). Thus, **15** was first subjected to alcoholysis with K₂CO₃ in allyl alcohol to give allyl carbonate **17** which, upon palladium-catalyzed reductive deallylation,¹⁹ afforded **18** in excellent yield. Jones oxidation of **18** gave the corresponding carboxylic acid which was then directly reacted with L-tyrosine *tert*-butyl ester²⁰ using EDCI as a dehydrating agent in the presence of *N*-methylmorpholine and 1-hydroxybenzotriazole²¹ to give viridifungin A tri-*tert*-butyl ester (**4**). Finally, cleavage of all *tert*-butyl ester groups in formic acid²² followed by reverse phase column chromatography furnished (-)-viridifungin A (**1**) in good yield. The spectral data (¹H and ¹³C NMR, IR, MS) and specific rotation[‡] were identical with those reported for natural viridifungin A.¹

In conclusion, we have accomplished the first total synthesis of (-)-viridifungin A from 3-butyn-1-ol in 22 steps in 5% overall



Scheme 2 Reagents and conditions: (i) K₂CO₃, CH₂=CHCH₂OH, -20 °C; (ii) HCO₂NH₄ (3 eq.), Ph₃P (0.3 eq.), Pd(PPh₃)₄ (0.1 eq.), THF; (iii) H₂CrO₄, aq. acetone, -10 °C; (iv) L-tyrosine *tert*-butyl ester, Me₂N(CH₂)₃N=C=NEt·HCl (EDCI), *N*-methylmorpholine, 1-hydroxybenzotriazole, DMF; (v) HCO₂H.

yield. This synthesis also provides a flexible route to various viridifungin analogues required for biological testing.

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Notes and references

[‡] [α]_D²⁰ -15.2° (c 0.93, MeOH) {lit.¹ [α]_D²⁵ -18.2° (c 2.37, MeOH)}; ¹H NMR (500 MHz, CD₃OD) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.28 (br s, 14H), 1.53 (m, 4H), 1.97 (m, 2H), 2.42 (t, *J* = 7.3 Hz, 3H), 2.43 (t, *J* = 7.3 Hz, 3H), 2.62 (d, *J* = 16.3 Hz, 1H), 2.86–2.92 (m, 3H), 3.10 (dd, *J* = 4.6, 14.1 Hz,

- 1H), 3.21 (d, $J = 8.0$ Hz, 1H), 4.60 (dd, $J = 4.8, 8.5$ Hz, 1H), 5.53 (m, 2H), 6.67 (d, $J = 8.5$ Hz, 2H), 7.02 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 14.4, 23.7, 24.8, 24.9, 29.8, 29.9, 30.0, 30.2, 30.3, 32.9, 33.5, 37.5, 43.1, 43.5 (2), 55.1, 57.7, 80.0, 116.2 (2), 124.5, 128.7, 131.4 (2), 137.6, 157.4, 173.6, 173.9, 174.5, 175.8, 214.6; FTIR (neat) 3748, 3656, 3363, 1712, 1523, 1454, 1232 cm^{-1} ; MS (EI) m/z 164 (100), 465, 511 [(M - 2H₂O - CO₂)⁺]; HRMS (EI) calcd for C₃₀H₄₁NO₆ [(M - 2H₂O - CO₂)⁺] 511.2934, found 511.2922; HRMS (FAB, NBA) calcd for C₃₁H₄₆NO₁₀ [(M + H)⁺] 592.3121, found 592.3110.
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