Total synthesis of viridiofungin A†

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Viridiofungin 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.

Viridiofungin A (**1**) was isolated from a strain of *Trichoderma viride* Pers., together with viridiofungin B and C, by Harris *et al.*[1] The viridiofungins 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 transferase[3] as well as squalene synthase[4] *in vitro* at the micromolar level. The viridiofungins 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 viridiofungin A (**1**) was determined by our enantiocontrolled synthesis of viridiofungin A trimethyl ester (**2**).[5] However, we could not achieve the synthesis of viridiofungin 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 viridiofungin A triester (**3**) based on ester dienolate [2,3]-Wittig rearrangement; however, they have not synthesized viridiofungin A (**1**). We describe herein the first total synthesis of viridiofungin 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 metathesis[7] 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-butyn-1-ol according to our previously established procedure (Scheme 1).[5] Katsuki–Sharpless asymmetric epoxidation[8] of **7** afforded epoxide **8** in 87% ee.[9] Successive Parikh–Doering oxidation,[10] $NaClO_2$ 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

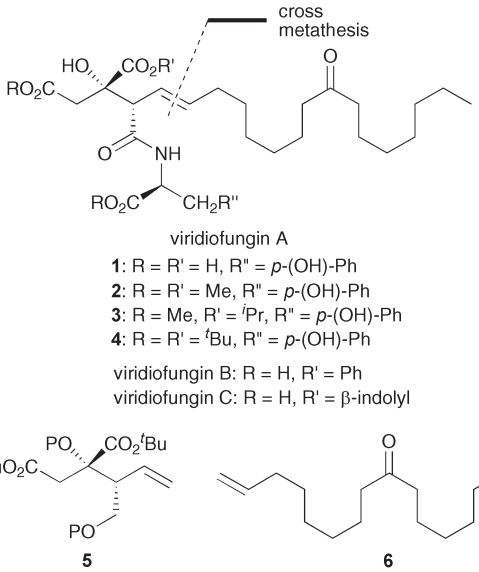
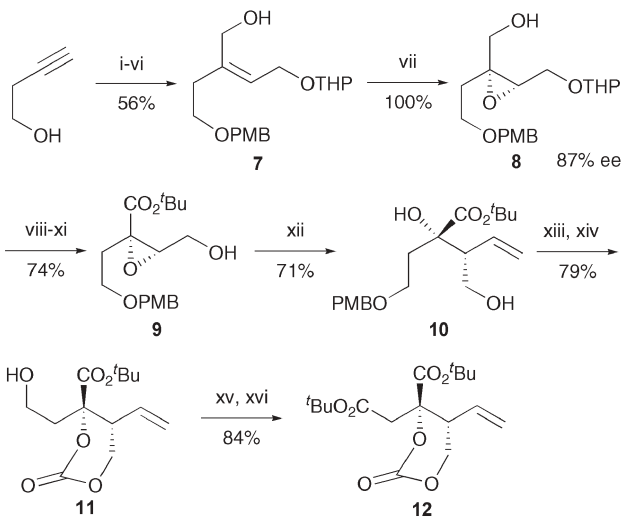


Fig. 1



Scheme 1 *Reagents and conditions*: (i) *p*-(MeO)$C_6H_4CH_2Cl$, NaH, $^nBu_4NI$, THF; (ii) ^{n}BuLi, $(CH_2O)n$, THF; (iii) Red-Al, Et_2O, 0 to 25 °C, then I_2, −50 to 25 °C; (iv) PPTS, DHP, CH_2Cl_2; (v) ^{t}BuLi, CO_2, Et_2O, −78 °C, then MeI, DMF; (vi) DIBAH, CH_2Cl_2, −78 °C; (vii) diethyl D-tartrate (0.3 eq.), $Ti(O^iPr)_4$ (0.25 eq.), ^{t}BuOOH (2 eq.), molecular sieves, CH_2Cl_2, −20 °C; (viii) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2; (ix) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH–H_2O (4:1); (x) *N*,*N*′-diisopropyl-*O*-2-*tert*-butylisourea, CH_2Cl_2; (xi) PPTS, MeOH; (xii) CH_2=CHMgBr (10 eq.), CuI (1 eq.), THF, −26 °C; (xiii) triphosgene, pyridine, THF; (xiv) DDQ, CH_2Cl_2–H_2O (20:1); (xv) H_2CrO_4, aq. acetone, −10 °C; (xvi) *N*,*N*′-diisopropyl-*O*-2-*tert*-butylisourea, CH_2Cl_2.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b5/b500660k/

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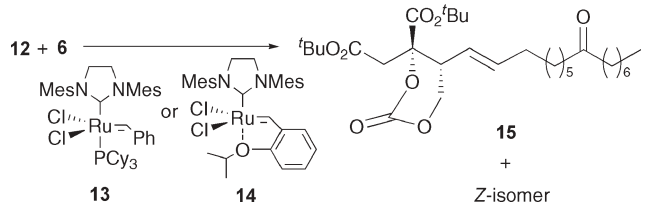
Table 1 Alkene cross metathesis of **12** with hexadec-15-en-8-one (**6**)[a]



Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield	
					15 + *Z*-isomer (%)[b] [*E*:*Z*][c]	**12** (%)
1	**13**	CH_2Cl_2	40	84	65 (86) [88:12]	24
2	**13**	Toluene	100	72	33 (65) [70:30]	49
3	**14**	CH_2Cl_2	40	16	48 (100) [85:15]	52
4	**14**	Toluene	100	72	57 (66) [89:11]	14

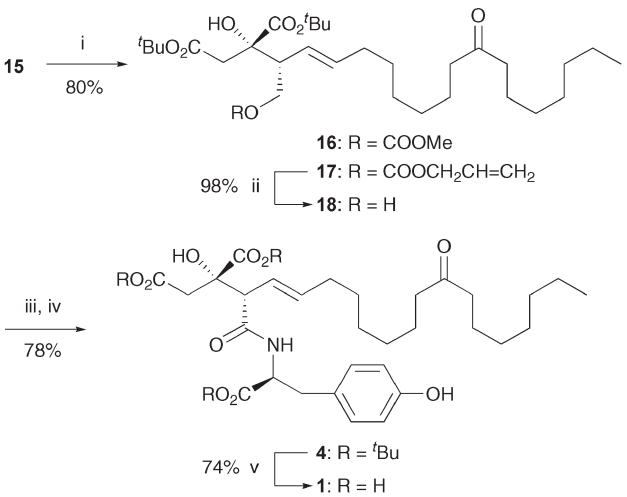
[a] All reactions were carried out using **12** (1 eq.), **13** or **14** (0.2 eq.) and **6** (2 eq.). [b] The yields in the parentheses were calculated based on recovered **12**. [c] Determined by ^{1}H NMR analysis.

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 catalyst[16] 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 CH_2Cl_2 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 viridiofungin A (**1**). Methanolysis of **15** in the presence of K_2CO_3 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 K_2CO_3 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 ester[20] using EDCI as a dehydrating agent in the presence of *N*-methylmorpholine and 1-hydroxybenzotriazole[21] to give viridiofungin A tri-*tert*-butyl ester (**4**). Finally, cleavage of all *tert*-butyl ester groups in formic acid[22] followed by reverse phase column chromatography furnished (−)-viridiofungin A (**1**) in good yield. The spectral data (^{1}H and ^{13}C NMR, IR, MS) and specific rotation‡ were identical with those reported for natural viridiofungin A.[1]

In conclusion, we have accomplished the first total synthesis of (−)-viridiofungin A from 3-butyn-1-ol in 22 steps in 5% overall yield. This synthesis also provides a flexible route to various viridiofungin analogues required for biological testing.



Scheme 2 *Reagents and conditions*: (i) K_2CO_3, CH_2=$CHCH_2OH$, −20 °C; (ii) HCO_2NH_4 (3 eq.), Ph_3P (0.3 eq.), $Pd(PPh_3)_4$ (0.1 eq.), THF; (iii) H_2CrO_4, aq. acetone, −10 °C; (iv) L-tyrosine *tert*-butyl ester, $Me_2N(CH_2)_3N$=C=NEt·HCl (EDCI), *N*-methylmorpholine, 1-hydroxybenzotriazole, DMF; (v) HCO_2H.

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Notes and references

‡ $[\alpha]_D^{26}$ −15.2° (*c* 0.93, MeOH) {lit.[1] $[\alpha]_D^{25}$ −18.2° (*c* 2.37, MeOH)}; ^{1}H NMR (500 MHz, CD_3OD) 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 [$(M - 2H_2O - CO_2)^+$]; HRMS (EI) calcd for $C_{30}H_{41}NO_6$ [$(M - 2H_2O - CO_2)^+$] 511.2934, found 511.2922; HRMS (FAB, NBA) calcd for $C_{31}H_{46}NO_{10}$ [$(M + H)^+$] 592.3121, found 592.3110.

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