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Synthesis of Viridiofungin A Trimethyl Ester and Determination of the Absolute Structure of Viridiofungin A[1]

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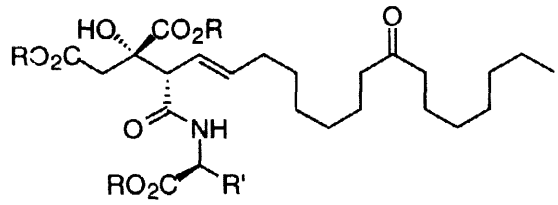
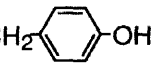
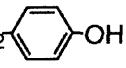
Abstract: Four diastereoisomeric trimethyl esters of viridiofungin A, a member of novel family of aminoacyl alkyl citrate compounds, were synthesized in a highly stereoselective manner and the absolute configuration of natural viridiofungin A was determined to be 3*S*,4*S*,2'*S*.

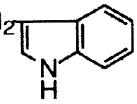
Viridiofungin A (**1**) was isolated from a strain of *Trichoderma viride* Pers. (Fungi, Hyphomycetes) together with viridiofungin B and C by researchers at Merck[2] after screening for substances that exhibit inhibitory activity against squalene synthase.[3] Although viridiofungins were found to be about four orders of magnitude less active than zaragozic acids in inhibition of squalene synthase, they have newly attracted much attention as novel potent inhibitors of sphingolipid synthesis.[4] These viridiofungins have unique structures consisting of a common alkylated citric acid moiety having a C-16 long chain and an aromatic amino acid residue such as tyrosine, phenylalanine, and tryptophan. The flat structures of these natural products were determined by spectroscopic analysis[2] but either absolute or relative structure has not been determined yet. We, therefore, need to develop a reliable synthetic route leading to their all diastereoisomers for the confirmation of the absolute structures. We describe herein the first synthesis of this novel family of aminoacyl alkyl citrate compounds, viridiofungin A trimethyl ester (**2**) and its three diastereoisomers, thereby establishing the absolute structure of viridiofungin A as depicted in **1**.



viridiofungin A (**1**): R = H, R' = 

2: R = CH_3, R' = 

viridiofungin B: R = H, R' = 

viridiofungin C: R = H, R' = 

p-Methoxybenzylation of 3-butyn-1-ol followed by reaction with paraformaldehyde in the presence of *n*-butyllithium gave propargylic alcohol **3**.[5] Successive treatment of **3** with Red-Al® and iodine[6] allowed stereo- and regioselective formation of (*Z*)-iodoalkene which was directly protected as its tetrahydropyranyl ether to give **4**. After treatment of **4** with *tert*-butyllithium, the resulting alkenyllithium was successively reacted with carbon dioxide and methyl iodide to give ester **5** almost quantitatively.[7] Upon sequential DIBAH reduction, *p*-

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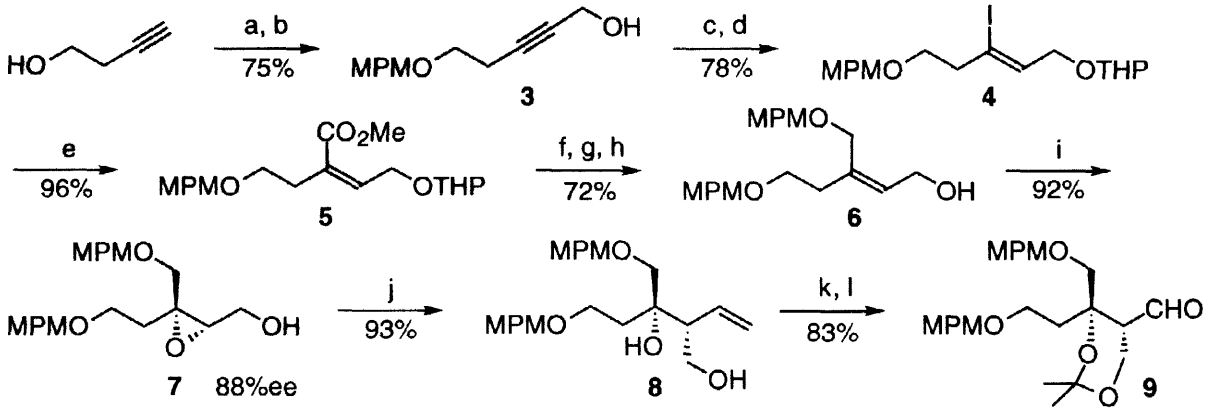
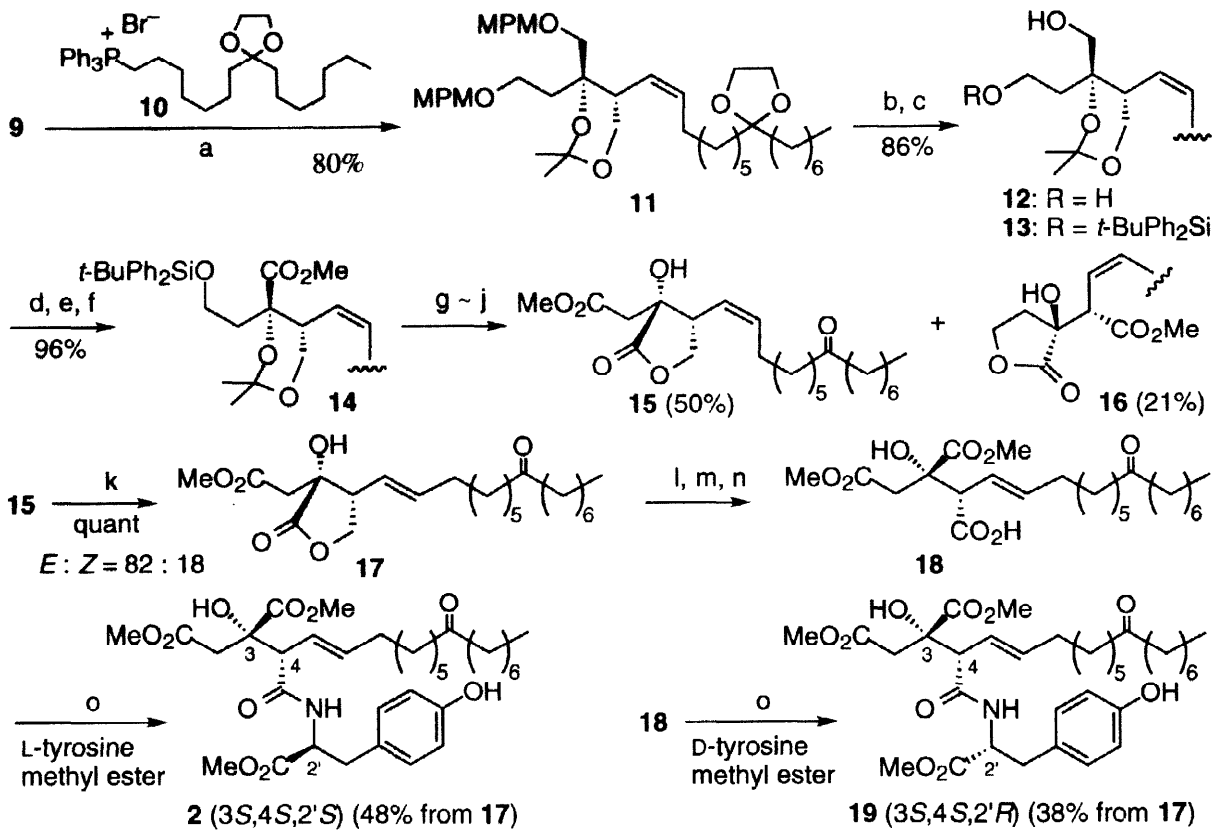
methoxybenzylation, and acidic methanolysis, the ester **5** gave trisubstituted allylic alcohol **6**. Katsuki-Sharpless catalytic asymmetric epoxidation[8] of **6** afforded epoxide **7** with enantiomeric purity[9] of 88% ee, $[\alpha]^{20}_D$ –19.8° (*c* 1.17, $CHCl_3$). Exposure of **7** to vinylmagnesium bromide in the presence of CuI caused regio- and stereoselective nucleophilic opening of the epoxide[10] to give diol **8**, $[\alpha]^{21}_D$ +15.6° (*c* 0.93, $CHCl_3$), exclusively. After protection of **8** as its acetonide, the alkenic double bond was cleaved by a sequence involving osmylation and $NaIO_4$ oxidation to yield (2*R*,3*S*)-aldehyde **9**.



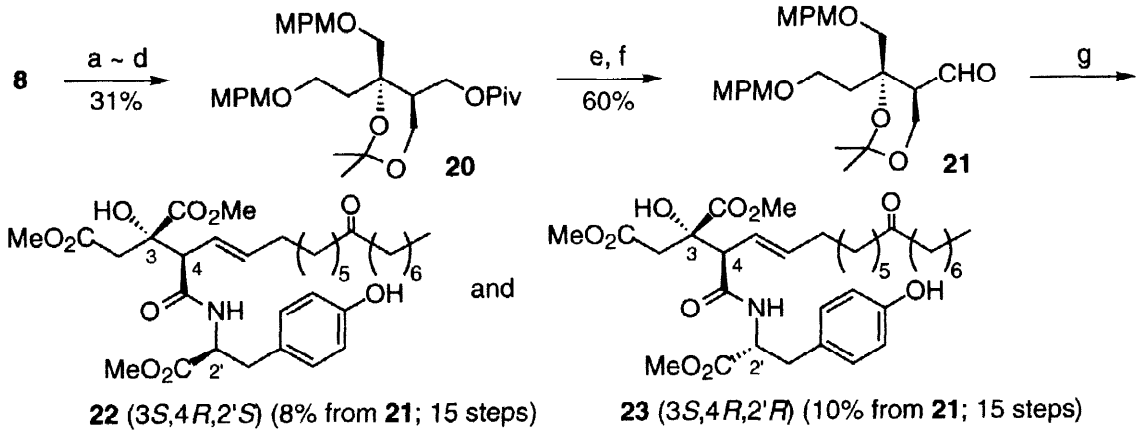
Scheme 1. (a) *p*-(MeO)$C_6H_4CH_2Cl$, NaH, *n*-Bu_4NI, THF; (b) *n*-BuLi, $(CH_2O)_n$, THF; (c) Red-Al®, Et_2O, 0 to 25 °C, then I_2, –50 to 25 °C; (d) PPTS, DHP, CH_2Cl_2; (e) *t*-BuLi, CO_2, Et_2O, –78 °C, then MeI, DMF; (f) DIBAH, CH_2Cl_2, –78 °C; (g) *p*-(MeO)$C_6H_4CH_2Cl$, NaH, *n*-Bu_4NI, THF, reflux; (h) PPTS, MeOH, reflux; (i) diisopropyl L-tartrate (0.09 equiv), Ti(O-*i*-Pr)$_4$ (0.07 equiv), *t*-BuOOH (2 equiv), 4 Å molecular sieves, CH_2Cl_2, –30 °C; (j) CH_2=CHMgBr, CuI, THF, –25 °C; (k) $(MeO)_2CMe_2$, PPTS, benzene, reflux; (l) OsO_4 (0.1 equiv), NMO, THF-H_2O (3 : 1), then $NaIO_4$.

Wittig reaction of **9** with the ylide, generated from **10** by the action of *n*-butyllithium, was conducted in THF at 0 °C to give (*Z*)-alkene **11**, $[\alpha]^{16}_D$ +20.1° (*c* 1.51, $CHCl_3$), stereoselectively.[11] Although Birch reduction of **11** gave the diol **12** quantitatively, all attempts at direct oxidation of its two hydroxymethyl groups to the carboxylic acids failed. However, their oxidations were eventually achieved by the following stepwise transformations. Crude diol **12** thus obtained was directly silylated with *tert*-butyldiphenylsilyl chloride. It is important to note that the silylation took place with complete siteselectivity to give mono-silyl ether **13**, $[\alpha]^{26}_D$ –0.6° (*c* 1.31, $CHCl_3$), exclusively and the other mono-silyl ether was not obtained in this particular case. Successive Swern oxidation, $NaClO_2$ oxidation, and esterification allowed quantitative conversion of **13** to ester **14**, $[\alpha]^{23}_D$ +17.6° (*c* 0.99, $CHCl_3$). A four-step sequence involving acid treatment to form the keto-lactone, HF-promoted desilylation, Jones oxidation, and esterification led **14** to lactone **15**, $[\alpha]^{19}_D$ +21.4° (*c* 0.87, $CHCl_3$) along with **16**, $[\alpha]^{28}_D$ –29.9° (*c* 1.00, $CHCl_3$).[12] Photo-isomerisation of the alkenic double bond was carried out at this stage and the desired *E*-isomer **17**, $[\alpha]^{19}_D$ –17.1° (*c* 0.39, $CHCl_3$), was obtained in a pure form[11] by separation of the resulting 82:18 *E*/*Z*-mixture using SiO_2 preparative TLC. Upon sequential saponification, esterification, and Jones oxidation, **17** gave carboxylic acid **18** which was directly subjected to condensation with L-tyrosine methyl ester. After considerable experimentation, it was found that the condensation was best accomplished using a water soluble carbodiimide as a dehydrating agent in the presence of 1-hydroxybenzotriazole and *N*-methylmorpholine[13] in DMF to furnish (3*S*,4*S*,2'*S*)-viridiofungin A trimethyl ester **2**, $[\alpha]^{26}_D$ –19.1° (*c* 0.43, MeOH). Similarly, (3*S*,4*S*,2'*R*)-viridiofungin A trimethyl ester **19**, $[\alpha]^{26}_D$ –15.5° (*c* 0.43, MeOH), was synthesized by condensation of **18** with D-tyrosine methyl ester.



Scheme 2. (a) *n*-BuLi, THF, 0 °C; (b) Li, THF-liq. NH_3, –33 °C; (c) *t*-$BuPh_2SiCl$, Et_3N, CH_2Cl_2; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 to 25 °C; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O (4:1); (f) CH_2N_2, Et_2O; (g) conc. HCl, *t*-BuOH; (h) 46% HF-MeCN (1 : 7); (i) H_2CrO_4, aq. acetone, –10 °C; (j) CH_2N_2, Et_2O; (k) hv, PhSSPh, *c*-hexane; (l) NaOH, MeOH; (m) CH_2N_2, Et_2O; (n) H_2CrO_4, aq. acetone, –10 °C; (o) $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, *N*-methylmorpholine, 1-hydroxybenzotriazole, DMF.

Furthermore, (3*S*,4*R*,2'*S*)-viridiofungin A trimethyl ester **22**, $[\alpha]^{27}_D$ +33.3° (*c* 0.47, MeOH), and (3*S*,4*R*,2'*R*)-viridiofungin A trimethyl ester **23**, $[\alpha]^{27}_D$ +31.6° (*c* 0.47, MeOH), were also synthesized from (2*S*,3*S*)-aldehyde **21** which was obtained from the diol **8** via **20**, $[\alpha]^{23}_D$ +5.0° (*c* 0.91, MeOH), as summarized in Scheme 3.



Scheme 3. (a) *t*-BuCOCl, Et_3N, CH_2Cl_2; (b) OsO_4 (0.1 equiv), NMO, THF-H_2O (3 : 1), then $NaIO_4$; (c) $NaBH_4$, MeOH; (d) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2; (e) NaOH, MeOH; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 to 25 °C; (g) as in Scheme 2.

Comparison ($^1H^{14}$ and ^{13}C NMR, $[\alpha]_D$) of these four diastereomers **2**, **19**, **22**, and **23** with viridiofungin A trimethyl ester, $[\alpha]^{25}_D$ –23.0° (*c* 0.47, MeOH), derived from natural viridiofungin A allowed us to conclude that viridiofungin A has 3S, 4S, and 2'S configurations.

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References and Notes:

(1) This report is dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.
(2) Harris, G. H.; Jones, E. T. T.; Meinz, M. S.; Nallin-Omstead, M.; Helms, G. L.; Bills, G. F.; Zink, D.; Wilson, K. E. *Tetrahedron Lett.* **1993**, *34*, 5235-5238.
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(5) All new compounds exhibited satisfactory spectral (^1H and ^{13}C NMR, IR, HRMS) data.
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(7) Palladium-catalyzed carbonylation of **4** in MeOH gave **5** in poor yield.
(8) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Org. Chem.* **1987**, *109*, 5765-5780.
(9) Determined by ^1H NMR (500 MHz) analysis of the corresponding (*R*)- and (*S*)-MTPA esters.
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(11) The stereochemistry was confirmed by NOE experiments (500 MHz ^1H NMR).
(12) The corresponding lactone-diol derived from **14** was partly isomerized to another lactone-diol during either HF-promoted desilylation or Jones oxidation.
(13) Kimura, T.; Takai, M.; Matsui, Y.; Morikawa, T.; Sakakibara, S. *Biopolymers* **1981**, *20*, 1823-1832.
(14) ^1H NMR (500 MHz, CD_3OD) spectra of **2**, **19**, **22**, and **23**.

2: δ 0.90 (t, 3H, *J* = 7.5 Hz), 1.29 (m, 14H), 1.53 (m, 4H), 1.98 (m, 2H), 2.43 (t, 4H, *J* = 7.5 Hz), 2.60 (d, 1H, *J* = 16.0 Hz), 2.87 (dd, 1H, *J* = 8.5, 14.5 Hz), 2.92 (d, 1H, *J* = 16.0 Hz), 3.07 (dd, 1H, *J* = 5.0, 14.5 Hz), 3.19 (d, 1H, *J* = 8.5 Hz), 3.64 (s, 3H), 3.70 (s, 3H), 3.71 (s, 3H), 4.61 (dd, 1H, *J* = 5.0, 8.5 Hz), 5.51 (m, 2H), 6.67 (d, 2H, *J* = 8.5 Hz), 6.98 (d, 2H, *J* = 8.5 Hz).

19: δ 0.90 (t, 3H, *J* = 7.0 Hz), 1.29 (m, 14H), 1.53 (quint, 4H, *J* = 6.5 Hz), 1.99 (q, 2H, *J* = 7.0 Hz), 2.44 (t, 4H, *J* = 8.0 Hz), 2.58 (d, 1H, *J* = 16.0 Hz), 2.80 (d, 1H, *J* = 16.0 Hz), 2.87 (dd, 1H, *J* = 9.0, 14.0 Hz), 3.09 (dd, 1H, *J* = 5.0, 14.0 Hz), 3.14 (d, 1H, *J* = 9.5 Hz), 3.62 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 4.61 (dd, 1H, *J* = 5.0, 9.0 Hz), 5.45 (dd, 1H, *J* = 9.0, 15.0 Hz), 5.56 (dt, 1H, *J* = 7.0, 15.0 Hz), 6.70 (d, 2H, *J* = 8.5 Hz), 7.00 (d, 2H, *J* = 8.5 Hz).

22: δ 0.90 (t, 3H, *J* = 7.5 Hz), 1.29 (m, 14H), 1.54 (m, 4H), 2.08 (q, 2H, *J* = 7.0 Hz), 2.43 (t, 2H, *J* = 7.5 Hz), 2.44 (t, 2H, *J* = 7.5 Hz), 2.65 (d, 1H, *J* = 15.5 Hz), 2.72 (d, 1H, *J* = 15.5 Hz), 2.87 (dd, 1H, *J* = 8.5, 14.0 Hz), 3.01 (dd, 1H, *J* = 5.5, 14.0 Hz), 3.30 (d, 1H, *J* = 9.5 Hz), 3.61 (s, 3H), 3.62 (s, 3H), 3.67 (s, 3H), 4.52 (dd, 1H, *J* = 6.0, 8.5 Hz), 5.49 (ddt, 1H, *J* = 1.5, 9.5, 15.0 Hz), 5.72 (dt, 1H, *J* = 7.0, 15.0 Hz), 6.69 (d, 2H, *J* = 8.5 Hz), 6.98 (d, 2H, *J* = 8.5 Hz).

23: δ 0.89 (t, 3H, *J* = 7.0 Hz), 1.29 (m, 14H), 1.53 (quint, 4H, *J* = 5.5 Hz), 2.05 (q, 2H, *J* = 6.5 Hz), 2.43 (t, 2H, *J* = 7.5 Hz), 2.44 (t, 2H, *J* = 7.5 Hz), 2.68 (d, 1H, *J* = 15.0 Hz), 2.73 (d, 1H, *J* = 15.0 Hz), 2.85 (dd, 1H, *J* = 8.5, 14.0 Hz), 3.00 (dd, 1H, *J* = 5.5, 14.0 Hz), 3.34 (d, 1H, *J* = 9.5 Hz), 3.62 (s, 3H), 3.68 (s, 3H), 3.72 (s, 3H), 4.56 (dd, 1H, *J* = 5.5, 8.0 Hz), 5.45 (ddt, 1H, *J* = 1.5, 9.5, 15.0 Hz), 5.66 (dt, 1H, *J* = 6.5, 15.0 Hz), 6.67 (d, 2H, *J* = 8.5 Hz), 6.95 (d, 2H, *J* = 8.5 Hz).