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Tetrahedron Letters 45 (2004) 6915–6918
Tetrahedron Letters

Total synthesis of (3*S*,4*S*,2′*S*)- and (3*R*,4*R*,2′*S*)-viridiofungin A triester

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Received 25 June 2004; revised 14 July 2004; accepted 19 July 2004
Available online 10 August 2004

Abstract—The total synthesis of an alkylcitrate secondary metabolite from the fungi *Trichoderma viride* is described. An ester dienolate [2,3]-Wittig rearrangement and a S. Julia-Kocienski olefination served as key C/C-connecting transformations. The highly convergent synthesis consists of a longest linear sequence of 17 steps.

Viridiofungin A **1** (VF_A) and a number of structurally related derivatives are secondary metabolites of the alkylcitrate family that have been isolated by bioassay-guided fractionation of the methyl ethyl ketone extracts of the soil fungi *Trichoderma viride*.[1] They originally attracted attention due to their potent, broad spectrum antifungal activity.[1] It was later shown that VF_A inhibits the squalene synthase of *Candida albicans* (IC_{50} 11.8 μM);[2] however, the antifungal activity is based on the inhibition of the serine palmitoyltransferase (*Candida albicans*: IC_{50} = 0.013 μg/mL).[3] Furthermore, it was found that VF_A inhibits the Ras farnesyl transferase in vitro (IC_{50} = 8 μM).[4] The structure of the viridiofungins was deduced from NMR studies and the absolute configuration of VF_A was assigned by an enantioselective total synthesis of VF_A trimethylester by Hatakeyama and co-workers.[5] Hatakeyama's total synthesis consists of a longest linear sequence of 27 steps and utilized a Sharpless asymmetric epoxidation to generate the crucial chiral carbon atoms at C-3 und C-4.

Our interest in a total synthesis of VF_A was sparked by its interesting biological activities and by its rather unusual structure featuring a highly functionalized polar head with two stereogenic centers, which is connected to a lipophilic chain by an isolated *E*-configured double bond.

The overall strategy rested on our finding that ester dienolates generated from α-allyloxy-substituted α,β-unsaturated esters are prone to undergo a diastereoselective [2,3]-Wittig rearrangement to afford highly ssubstituted 1,5-hexadienes.[6] Accordingly, we expected that the enol ether **3** should be accessible from the allyl vinyl ether **5** by an ester dienolate [2,3]-Wittig rearrangement (Scheme 1). Although racemic, the enol ether **3** would contain the three required carboxylic groups in distinguishable oxidation states. We envisioned that this would significantly ease the chemoselective generation of the two carboxylic acid groups and the amide function in VF_A. The second crucial step was expected to be the generation of the isolated *E*-configured double bond between C-5 and C-6, which connects the polar head with the lipophilic chain of VF_A. The attachment of the enantiomerically pure amino acid to the racemic carbon skeleton of VF_A would be the final step followed by the separation of the thereby generated diastereomers by chromatography.

The realization of the synthetic strategy is outlined in Scheme 2. The pivotal starting material for the sequence, allyl vinyl ether **5**, was synthesized in five steps according to our previously published procedure.[7] Treatment of (*Z*,*Z*)-**5** with LDA followed by warming the reaction mixture to −10 °C afforded the rearrangement product **3** with a diastereoselectivity of 95/5 in favor of the *syn*-configured diastereomer.[8] The observed diastereoselectivity may be explained assuming that the $BnOCH_2$ substituent on the allylic ether double bond is preferentially directed toward the convex face of the bicyclic transition state **6**. Unfortunately, even after considerable

Keywords: Total synthesis; [2,3]-Wittig rearrangement; Viridiofungin.
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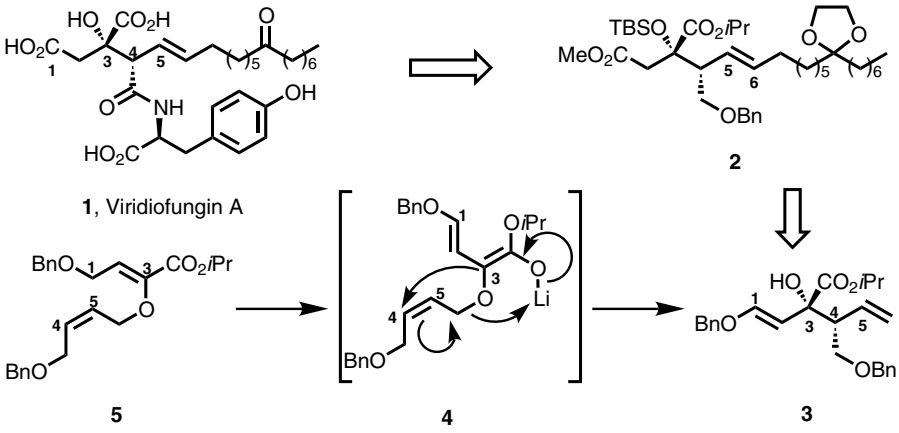
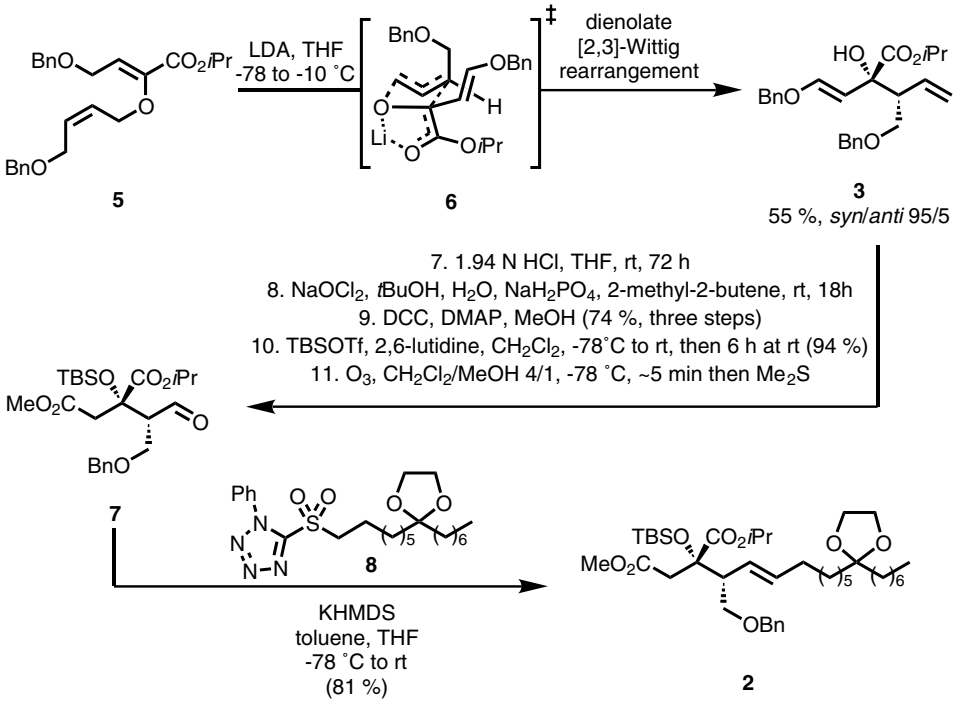
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.07.086



Scheme 1. Retrosynthetic analysis of viridiofungin A based on the application of the ester dienolate [2,3]-Wittig rearrangement of the α-allyloxy-substituted α,β-unsaturated ester **5** via the ester dienolate **4** to afford the highly functionalized 1,5-hexadiene **3**.

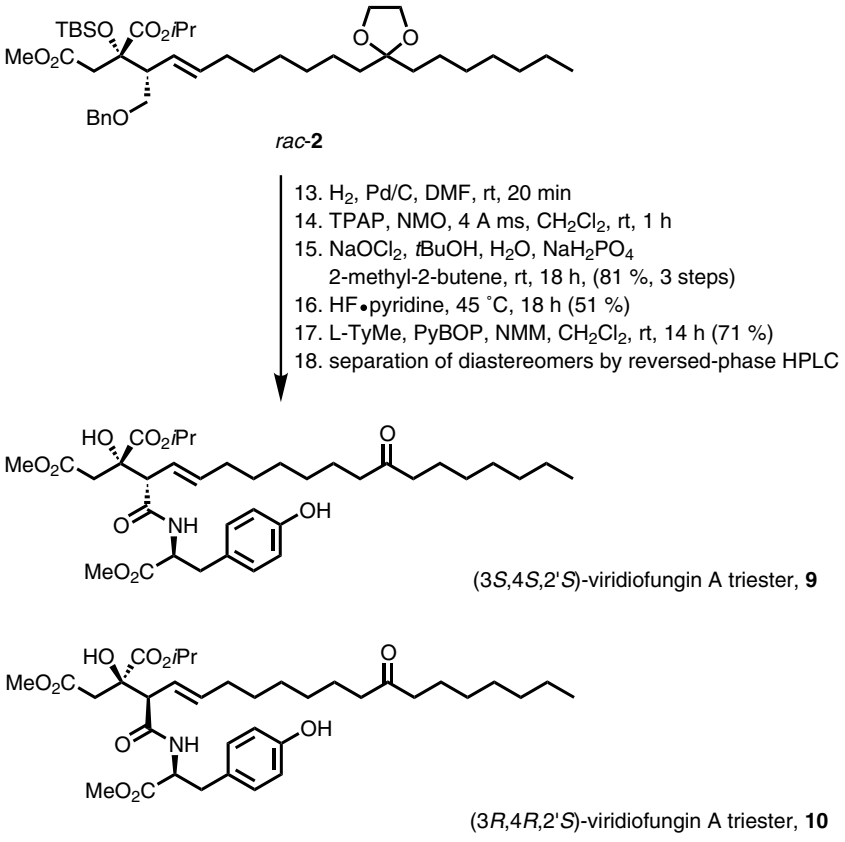


Scheme 2. LDA: lithium diisopropylamide, DCC: dicyclohexylcarbodiimide, DMAP: 4-(*N*,*N*-dimethylamino)pyridine, TBSOTf: *tert*-$BuMe_2SiO$-SO_2CF_3, KHMDS: $KN(SiMe_3)_2$.

experimentation, we were unable to improve the chemical yield of the [2,3]-Wittig rearrangement. However, the rearrangement of **5** can reliably be performed on a 5 g scale with a constantly high diastereoselectivity.

The enol ether **3** was then hydrolyzed to afford the corresponding aldehyde that was oxidized to the acid. The acid was converted into the methyl ester using DCC/DMAP activation.[9] The tertiary hydroxyl function was then protected as a *tert*-butyldimethylsilylether.[10] Ozonolysis of the double bond provided the unstable aldehyde **7** that was used immediately without further purification. The S. Julia-Kocienski olefination[11] of the aldehyde **7** with the deprotonated sulfone **8**[12] afforded the complete carbon framework of VF_A as single double bond isomer.[13]

Having completely assembled the carbon skeleton of VF_A (Scheme 2), it was next required to introduce the amino acid residue (Scheme 3). Therefore, the benzyl protecting group had to be removed in the presence of the isolated double bond. This task was most conveniently accomplished with molecular hydrogen in the presence of palladium on carbon. It was necessary to control the reaction time carefully in order to avoid double bond hydrogenation. The primary alcohol was immediately oxidized using a two-step protocol to afford the corresponding acid.[14,15] Removal of the TBS and the



Scheme 3. TPAP: Tetrapropylammonium perruthenate, NMO: *N*-methylmorpholine *N*-oxide, L-TyMe: L-tyrosine methyl ester, PyBOP: benzotriazolyloxy-tris(pyrrolidino)-phosphonium hexafluorophosphate, NMM: *N*-methylpyrrolidine. Preparative HPLC: column VYDAC 208TP1030–C8 (10 μm), 30 × 250 mm, eluent (isocratic A/B 57/43): solvent A: H_2O + 5% CH_3CN + 15% CH_3OH + 0.1% TFA, solvent B: CH_3CN + 0.1% TFA, 40 mL/min, t_R (**9**): 58 min, t_R (**10**): 63 min.

dioxolane protecting groups was accomplished with HF·pyridine in moderate yield. Finally, amide formation between the racemic acid and L-tyrosine methyl ester according to Castro et al.[16] afforded two diastereomers, which were separated by preparative reversed-phase HPLC to provide the (3*S*,4*S*,2′*S*)-VF_A triester (**9**)[17] and the (3*R*,4*R*,2′*S*)-VF_A triester (**10**)[18] as single diastereo- and enantiomers.

In summary, a short and convergent synthesis of a triester of viridiofungin A (**9**) and the nonnatural diastereomer **10** has been executed. The ester dienolate [2,3]-Wittig rearrangement was utilized to diastereoselectively synthesize the polar head of the viridiofungins in moderate yield. Work aimed at the synthesis of other natural and nonnatural viridiofungins is currently under way.

Acknowledgements

Financial support by the DFG and the FCI is gratefully acknowledged. Access to HPLC equipment was provided by the Knölker research group. A.P. thanks Dr. Georg Schlechting for technical advice. Early contributions of Regina Czerwonka to this project are gratefully appreciated.

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7. The synthesis of (*Z*,*Z*)-**5** was performed according to Hiersemann, M. *Synthesis* **2000**, 1279–1290. Subsequent separation of vinyl ether double bond isomers by preparative HPLC. Details will be published elsewhere.
8. The assignment of the relative configuration was made in analogy to our previous work concerning the relationship between the allylic ether double bond configuration of the α-allyloxy-substituted α,β-unsaturated ester and the relative configuration of the product of the ester dienolate [2,3]-Wittig rearrangement, see: Hiersemann, M.

Tetrahedron **1999**, *55*, 2625–2638. Furthermore, comparison of the spectroscopic data of our synthetic viridiofungin A and the spectroscopic data provided by Hatakeyama et al. support the assignment of the relative configuration of **3**.

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12. The sulfone **8** was prepared in 60% overall yield starting from 1,3-dithiane by a consecutive alkylation with $CH_3(CH_2)_6Br$, then $TPSO(CH_2)_7I$ followed by desilylation, Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol and oxidation with $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$, H_2O_2.
13. The corresponding *Z*-configured double bond diastereomer was independently generated by a Wittig reaction of the aldehyde **7** and the corresponding phosphonium ylide. Comparison of NMR data support the conclusion of a very high diastereoselectivity in favor of the *E*-configured double bond isomer for the S. Julia-Kocienski olefination.
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17. (3*S*,4*S*,2′*S*)-VF_A triester (**9**): ^{1}H NMR δ (500 MHz, $CDCl_3$) 6.95 (d, J = 8.4 Hz, 2H, 5′-H), 6.76 (d, J = 8.5 Hz, 2H, 6′-H), 6.67 (d, J = 7.9 Hz, 1H, NH), 6.34 (s, 1H, Ph–OH), 5.63 (ddd, J = 15.2, 6.6, 6.6 Hz, 1H, 6-H), 5.49 (dd, J = 15.3, 9.6 Hz, 1H, 5-H), 5.05 (sept, J = 6.3 Hz, 1H, CO_2iPr–CH), 4.74 (ddd, J = 7.1, 7.0, 5.1 Hz, 1H, 2′-H), 4.49 (s, 1H, 3-OH), 3.72 (s, 3H, 1′-CO_2CH_3), 3.65 (s, 3H, 1-CO_2CH_3), 3.16 (d, J = 9.5 Hz, 1H, 4-H), 3.09 (dd, J = 14.1, 4.9 Hz, 1H, 3′-CH_2), 3.00 (dd, J = 14.1, 6.8 Hz, 1H, 3′-CH_2), 2.85 (dd, J = 16.0 Hz, 1H, 2-CH_2), 2.68 (dd, J = 16.0 Hz, 1H, 2-CH_2), 2.42 (t, J = 7.2 Hz, 2H, 12- or 14-CH_2), 2.41 (t, J = 7.4 Hz, 2H, 12- or 14-CH_2), 2.01–1.92 (m, 2H, 7-CH_2), 1.59–1.48 (m, 4H, 11- and 15-CH_2), 1.34–1.18 (m, 20H, O*i*Pr–CH_3, 8-,9-,10-CH_2 and 16-,17-,18-,19-CH_2), 0.86 (t, J = 6.9 Hz, 3H, 20-CH_3); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 213.4 (13-C=O), 172.2 (CO_2iPr), 171.6 (1′-CO_2CH_3), 170.6 (CONH), 170.5 (1-CO_2CH_3), 155.4 (7′-aryl-COH), 137.8 (6-CH), 130.4 (2 × 5′-aryl-CH), 127.3 (4′-aryl-C), 122.4 (5-CH), 115.5 (2 × 6′-aryl-CH), 76.1 (3-C), 70.2 (O*i*Pr–CH), 57.6 (4-CH), 53.3 (2′-CH), 52.3 (CO_2CH_3), 51.8 (CO_2CH_3), 43.0 (12- or 14-CH_2), 42.7 (12- or 14-CH_2), 41.6 (2-CH_2), 36.6 (3′-CH_2), 32.5 (7-CH_2), 31.7 (18-CH_2), 29.7 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 23.9 (11- or 15-CH_2), 23.5 (11- or 15-CH_2), 22.6 (19-CH_2), 21.7 (O*i*Pr–CH_3), 21.6 (O*i*Pr–CH_3), 14.1 (20-CH_3); IR (in substance) ν 3334, 2930–2850, 2465, 2250, 2070, 1740; Anal. Calcd for $C_{36}H_{55}NO_{10}$: C, 65.33, H, 8.38. Found: C, 65.47, H, 8.48; $[\alpha]_D^{25}$ −6.6 (*c* 0.15, $CHCl_3$), literature for trimethylester: $[\alpha]_D^{25}$ −23.0 (*c* 0.47, MeOH).
18. (3*R*,4*R*,2′*S*)-VF_A triester (**10**): ^{1}H NMR δ (500 MHz, $CDCl_3$) 7.05 (d, J = 7.7 Hz, 1H, NH), 7.01 (br s, 1H, Ph–OH), 6.94 (d, J = 8.5 Hz, 2H, 5′-H), 6.77 (d, J = 8.5 Hz, 2H, 6′-H), 5.55 (ddd, J = 15.2, 6.4, 6.4 Hz, 1H, 6-H), 5.23 (dd, J = 15.3, 9.6 Hz, 1H, 5-H), 5.03 (sept, J = 6.2 Hz, 1H, O*i*Pr–CH), 4.73 (ddd, J = 7.9, 7.9, 4.7 Hz, 1H, 2′-H), 4.23 (s, 1H, 3-OH), 3.75 (s, 3H, 1′-CO_2CH_3), 3.64 (s, 3H, 1-CO_2CH_3), 3.15–3.08 (m, 1H, 3′-CH_2), 3.13 (d, J = 9.5 Hz, 1H, 4-H), 3.05 (d, J = 16.3 Hz, 1H, 2-CH_2), 2.89 (d, J = 16.1 Hz, 1H, 2-CH_2), 2.91–2.86 (m, 1H, 3′-CH_2) 2.45 (t, J = 7.0 Hz, 2H, 12- or 14-CH_2), 2.43 (t, J = 7.5 Hz, 2H, 12- or 14-CH_2), 1.92–1.83 (m, 2H, 7-CH_2), 1.62–1.48 (m, 4H, 11-, 15-CH_2), 1.3–1.15 (m, 20H, O*i*Pr–CH_3, 8-, 9-, 10-, 16-, 17-, 18-, 19, -CH_2), 0.86 (t, J = 6.9 Hz, 3H, 20-CH_3); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 214.3 (13-C=O), 172.3 (CO_2iPr), 171.9 (1′-CO_2CH_3), 170.6 (CONH), 170.4 (1-CO_2CH_3), 155.6 (7′-aryl-COH), 137.1 (6-CH), 130.2 (2 × 5′-aryl-CH), 127.1 (4′-aryl-C), 121.6 (5-CH), 115.4 (2 × aryl-6′-CH), 75.9 (3-C), 70.5 (O*i*Pr–CH), 58.0 (4-CH), 53.2 (2′-CH), 52.4 (CO_2CH_3), 51.8 (CO_2CH_3), 43.0 (12- or 14-CH_2), 42.7 (12- or 14-CH_2), 41.0 (2-CH_2), 36.5 (3′-CH_2), 32.3 (7-CH_2), 31.6 (18-CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 23.9 (11- or 15-CH_2), 23.4 (11- or 15-CH_2), 22.6 (19-CH_2), 21.8 (O*i*Pr–CH_3), 21.5 (O*i*Pr–CH_3), 14.0 (20-CH_3); IR (in substance) ν 3370, 2930–2855, 2490, 2250, 2070, 1740; Anal. Calcd for $C_{36}H_{55}NO_{10}$: C, 65.33, H, 8.38. Found: C, 65.06, H, 8.48; $[\alpha]_D^{25}$ +52.9 (*c* 0.51, $CHCl_3$).