An Enantioselective Synthesis of (11*R*,12*S*,13*S*,9*Z*,15*Z*)-9,12,13-Trihydroxyoctadeca-9,15-dienoic Acid, a Self-defensive Substance against Rice Blast Disease

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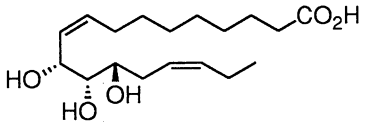
(11*R*,12*S*,13*S*,9*Z*,15*Z*)-9,12,13-Trihydroxyoctadeca-9,15-dienoic acid, a self-defensive substance against rice blast disease, has been synthesized in an enantiomerically pure form in 8% overall yield from (2*E*,5*E*)-1,2-dibenzyloxy-2,5-heptadien-4-ol.

Oxygenated metabolites of unsaturated fatty acids are known to play important roles in biological systems either in animals or in plants.[1] For example, (11*R*,12*S*,13*S*,9*Z*,15*Z*)-9,12,13-trihydroxyoctadeca-9,15-dienoic acid (**1**), a C_{18} fatty acid isolated from rice plants suffering from rice blast disease caused by *Pyricularia oryzae*, was proved to be a self-defensive substance against the fungus.[2] Because of low availability of this family of fatty acids from natural sources, much effort has been devoted to developing an efficient method for their syntheses to make biological evaluation possible.[3]

Recently, we have developed[4] an efficient method for the preparation of enantiomerically pure compounds of the general structure **2** from (2*E*,5*E*)-1,2-dibenzyloxy-2,5-heptadien-4-ol (**3**). In order to demonstrate the versatility of this method, we have investigated an enantioselective synthesis of (11*R*,12*S*,13*S*,9*Z*,15*Z*)-9,12,13-trihydroxyoctadeca-9,15-dienoic acid (**1**).



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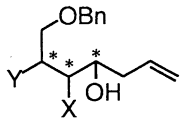
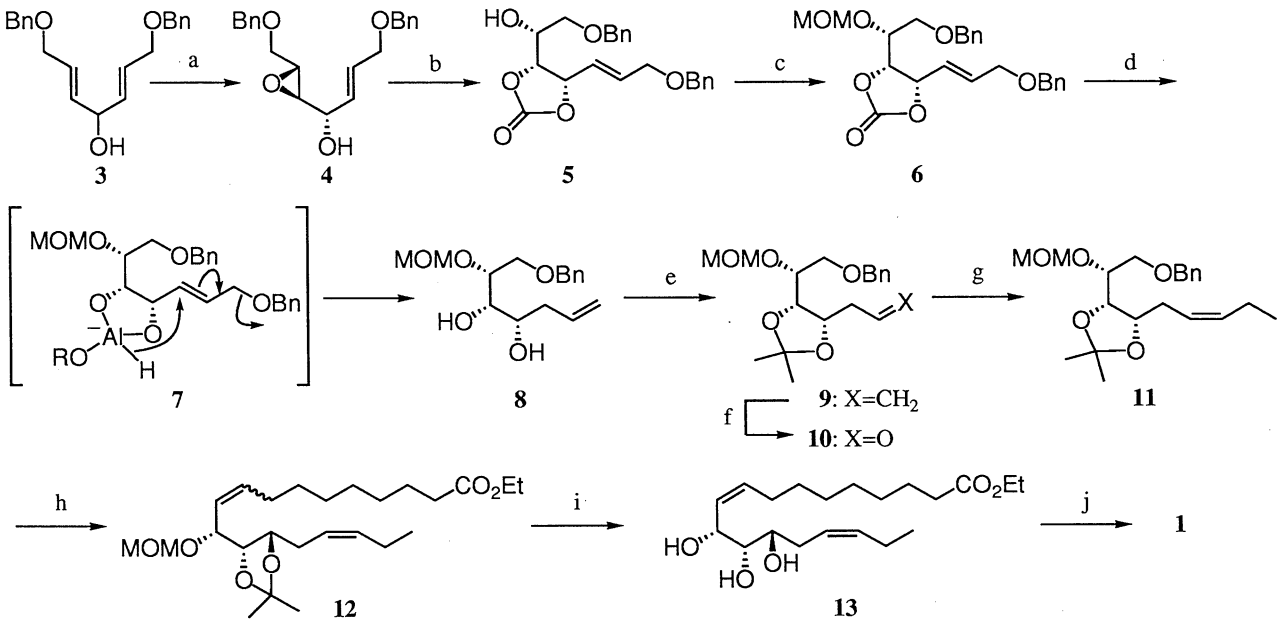


2: X or Y=OH
X=Y=OH

σ-Symmetrical (2*E*,5*E*)-1,2-dibenzyloxy-2,5-heptadien-4-ol (**3**) was first converted into the optically pure epoxy alcohol **4** in 62% yield by the Katsuki-Sharpless catalytic asymmetric epoxidation[5] followed by the modified Mitsunobu reaction[6] according to the previously established procedure.[4] Reaction of **4** with phenyl isocyanate and treatment[7] of the corresponding urethane with BF_3·Et_2O followed by 1 M H_2SO_4 gave the cyclic carbonate **5**,[8] $[\alpha]_D^{22}$ +1.3° (*c* 1.65, $CHCl_3$), in 85% yield. After protection of **5** as its methoxymethyl ether, treatment of the MOM ether **6**,[9] $[\alpha]_D^{22}$ –11.6° (*c* 1.15, $CHCl_3$), with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) in boiling toluene



Scheme 1. (a) (i) diisopropyl D-tartrate (9 mol%), Ti(O-*i*-Pr)$_4$ (7 mol%), *t*-BuOOH (2 equiv.), 4A molecular sieves, CH_2Cl_2, –25 °C, (ii) diethyl azodicarboxylate (DEAD) (5 equiv.), Ph_3P (5 equiv.), *p*-$(NO_2)C_6H_4CO_2H$ (4.4 equiv.), toluene, –20 °C, (iii) K_2CO_3, MeOH; (b) (i) PhNCO, pyridine, CH_2Cl_2, (ii) BF_3·Et_2O (1.4 equiv.), Et_2O, –20 °C to RT, then 1 M H_2SO_4; (c) $MeOCH_2Cl$, *i*-Pr_2EtN, CH_2Cl_2; (d) Red-Al® (5 equiv.), toluene, reflux; (e) $(MeO)_2CMe_2$, PPTS (catalyst), CH_2Cl_2; (f) (i) OsO_4 (10 mol%), NMO (2 equiv.), (ii) $Pb(OAc)_4$, THF, –25 °C; (g) $[Ph_3PCH_2CH_2CH_3]^+Br^-$, *n*-BuLi, toluene, 0 °C, then add aldehyde, –78 °C; (h) (i) Li, liq. NH_3, (ii) $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C, then Et_3N, (iii) $[Ph_3P(CH_2)_8CO_2Et]^+Br^-$, $KN(SiMe_3)_2$, THF, 0 °C, then add aldehyde, –78 °C; (i) PPTS (catalyst), EtOH, reflux; (j) KOH, aq. MeOH.

caused reduction of the carbonate moiety and also concomitant reductive cleavage of the benzyloxy group as in **7** to give the diol **8**,[10] $[\alpha]_D^{22}$ –18.6° (*c* 1.04, $CHCl_3$), in 85% yield. Protection of **8** as its acetonide followed by oxidative cleavage of the olefinic double bond of **9**, $[\alpha]_D^{22}$ –30.2° (*c* 0.87, $CHCl_3$), *via* dihydroxylation and lead tetraacetate oxidation afforded the aldehyde **10**. Without purification, the aldehyde **10** was directly subjected to Wittig reaction with ethylidenetriphenylphosphorane to give the olefin **11**,[11] $[\alpha]_D^{22}$ –29.9° (*c* 1.35, $CHCl_3$), as an inseparable 30:1 mixture[12] of *Z*- and *E*-isomers in 74% overall yield. Upon sequential Birch reduction , Swern oxidation, and Wittig reaction with ethyl 9-(triphenylphosphorylidene)-nonanoate,[3g] the compound **11** was converted into the ester **12** in 58% yield. The *Z*/*E* ratio of the newly formed olefinic double bond was shown to be 8:1 by its ^{1}H NMR (500 MHz) spectrum. Treatment of **12** with a catalytic amount of PPTS in boiling ethanol followed by silica gel column chromatography[13] gave the triol **13**,[14] $[\alpha]_D^{22}$ –16.8° (*c* 0.37, $CHCl_3$), in 41% yield. Finally, saponification of **13** with potassium hydroxide in aqueous methanol furnished (11*R*,12*S*,13*S*,9*Z*,15*Z*)-9,12,13-trihydroxy-octadeca-9,15-dienoic acid (**1**) in quantitative yield. The synthetic substance, $[\alpha]_D^{22}$ –15.8° (*c* 1.00, $CHCl_3$) [lit.[3g] $[\alpha]_D^{20}$ –16.4° (*c* 0.4, $CHCl_3$)], exhibited spectral properties (^{1}H NMR, IR, MS) in accord with those reported.[3g]

The present work illustrates a new methodology of general value for the synthesis of oxygenated unsaturated fatty acids related to **1** in enantiomerically pure forms.

References and Notes

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8 All new compounds reported herein exhibited satisfactory spectral (^{1}H NMR, IR, MS) and analytical (HR MS) data.

9 **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31 (3H, s), 3.62 (1H, dd, *J*=4.2 and 10.3 Hz), 3.73 (1H, dd, *J*=4.7 and 10.3 Hz), 3.93 (1H, dt, *J*=6.5 and 4.4 Hz), 4.03 (2H, m), 4.47 (1H, d, *J*=11.9 Hz), 4.52 (2H, s), 4.55 (1H, d, *J*=11.9 Hz), 4.64 (1H, d, *J*=6.8 Hz), 4.68 (1H, d, *J*=6.8 Hz), 4.92 (1H, dd, *J*=6.5 and 7.7 Hz), 5.21 (1H, ddt, *J*=5.6, 7.7 and 1.2 Hz), 5.98 (1H, m), 7.30-7.40 (5H, m).

10 **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (1H, dt, *J*=14.2 and 7.7 Hz), 2.47 (1H, d, *J*=4.3Hz), 2.56 (1H, m), 2.84 (1H, d, *J*=4.8 Hz), 3.39 (3H, s), 3.65-3.77 (3H, m), 3.81 (1H, dd, *J*=5.2 and 10.1 Hz), 3.96 (1H, q, *J*=4.3 Hz), 4.54 (1H, d, *J*=11.8 Hz), 4.60 (1H, d, *J*=11.8 Hz), 4.71 (1H, d, *J*=6.8 Hz), 4.75 (1H, d, *J*=6.8 Hz), 5.13 (1H, d, *J*=1.4 Hz), 5.18 (1H, dq, *J*=8.0 and 1.4 Hz), 5.89 (1H, m), 7.36 (5H, br s).

11 **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, t, *J*=7.5 Hz), 1.34 (3H, s), 1.41 (3H, s), 2.10 (2H, quint, *J*=7.4 Hz), 2.23-2.45 (2H, m), 3.38 (3H, s), 3.67 (1H, dd, J=5.4 and 10.9 Hz), 3.80-3.85 (2H, m), 4.17-4.28 (2H, m), 4.58 (2H, S), 4.71 (1H, d, *J*=6.8 Hz), 4.85 (1H, d, *J*=6.8 Hz), 5.40-5.56 (2H, m), 7.29-7.35 (5H, m).

12 Determined by ^{1}H NMR (300 MHz) analysis.

13 Other olefinic geometrical isomers were also obtained and not fully characterized.

14 **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, t, *J*=7.3 Hz), 1.25 (3H, t, *J*=7.3 Hz), 1.21-1.42 (8 H, m), 1.61 (2H, br quint, *J*=7.3 Hz), 2.00-2.22 (4H, m), 2.23-2.43 (9H, m), 2.50 (1H, m), 2.83 (1H, br s), 3.49 (1H, dd, J=7.3 and 6.2 Hz), 3.69 (1H, dt, *J*=3.0 and 7.3 Hz), 4.12 (2H, q, J=7.3 Hz), 4.61 (1H, dd, *J*=6.2 and 9.0 Hz), 5.43 (1H, m), 5.50 (1H, ddt, *J*=11.0, 9.0, and 1.4 Hz), 5.63 (1H, m), 5.71 (1H, ddt, *J*=11.0, 7.3, and 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 14.3, 20.8, 24.9, 28.0, 29.0, 29.5, 31.5, 34.4, 60.3, 69.9, 73.2, 75.3, 124.0, 127.9, 135.9, 136.0, 174.1.