

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

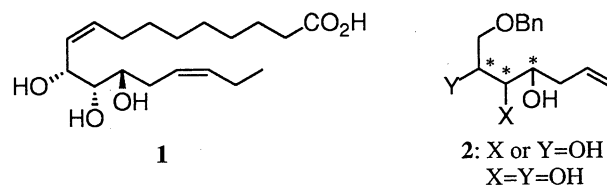
Susumi Hatakeyama,* Kennichiro Kojima, Hiroko Fukuyama, and Hiroshi Irie*
Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852

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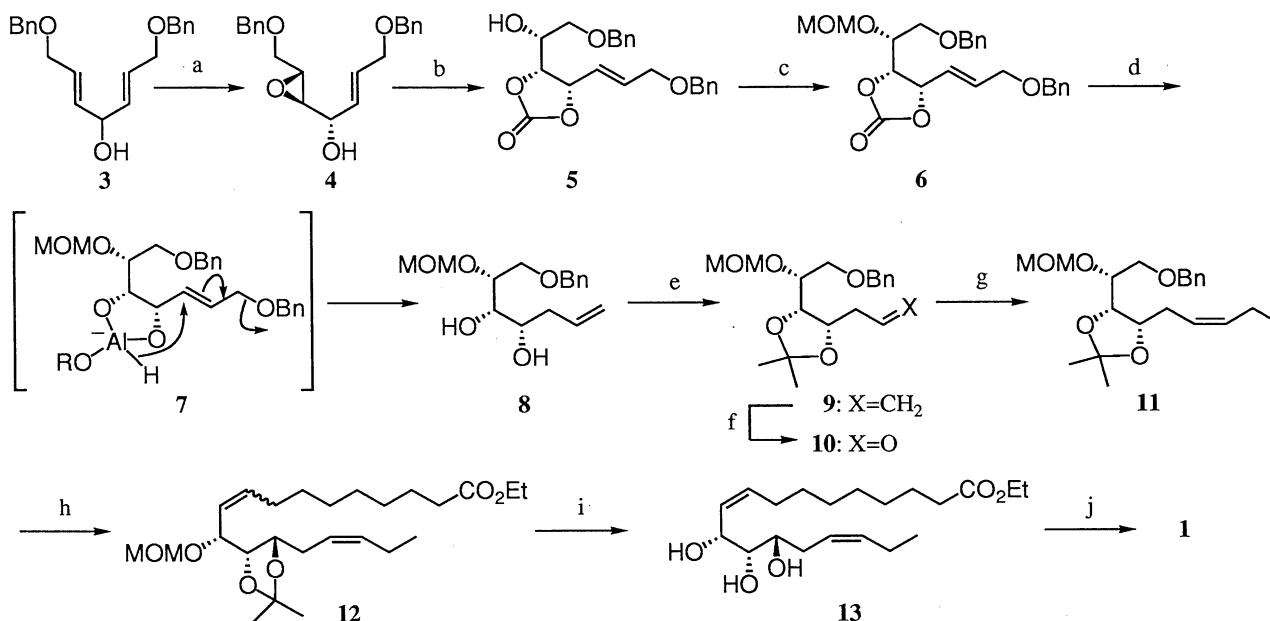
(11*R*,12*S*,13*S*,9*Z*,15*Z*)-9,12,13-Trihydroxyoctadeca-9,15-dienoic acid, a self-defensive substance against rice blast disease, has been synthesized in an enantiomerically pure form in 8% overall yield from (2*E*,5*E*)-1,2-dibenzyloxy-2,5-heptadien-4-ol.

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 C₁₈ 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 developed⁴ 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**).



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 epoxidation⁵ followed by the modified Mitsunobu reaction⁶ according to the previously established procedure.⁴ Reaction of **4** with phenyl isocyanate and treatment⁷ of the corresponding urethane with BF₃·Et₂O followed by 1 M H₂SO₄ gave the cyclic carbonate **5**,⁸ [α]_D²² +1.3° (*c* 1.65, CHCl₃), in 85% yield. After protection of **5** as its methoxymethyl ether, treatment of the MOM ether **6**,⁹ [α]_D²² -11.6° (*c* 1.15, CHCl₃), 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, CH₂Cl₂, -25 °C, (ii) diethyl azodicarboxylate (DEAD) (5 equiv.), Ph₃P (5 equiv.), *p*-(NO₂)C₆H₄CO₂H (4.4 equiv.), toluene, -20 °C, (iii) K₂CO₃, MeOH; (b) (i) PhNCO, pyridine, CH₂Cl₂, (ii) BF₃·Et₂O (1.4 equiv.), Et₂O, -20 °C to RT, then 1 M H₂SO₄; (c) MeOCH₂Cl, *i*-Pr₂EtN, CH₂Cl₂; (d) Red-Al® (5 equiv.), toluene, reflux; (e) (MeO)₂CMe₂, PPTS (catalyst), CH₂Cl₂; (f) (i) OsO₄ (10 mol%), NMO (2 equiv.), (ii) Pb(OAc)₄, THF, -25 °C; (g) [Ph₃PCH₂CH₂CH₃]⁺Br⁻, *n*-BuLi, toluene, 0 °C, then add aldehyde, -78 °C; (h) (i) Li, liq. NH₃, (ii) (COCl)₂, DMSO, CH₂Cl₂, -60 °C, then Et₃N, (iii) [Ph₃P(CH₂)₈CO₂Et]⁺Br⁻, KN(SiMe₃)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 $[\alpha]_D^{22} -18.6^\circ$ (c 1.04, CHCl_3), in 85% yield. Protection of **8** as its acetone followed by oxidative cleavage of the olefinic double bond of **9**, $[\alpha]_D^{22} -30.2^\circ$ (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 ethylenetriphenylphosphorane to give the olefin **11**,¹¹ $[\alpha]_D^{22} -29.9^\circ$ (c 1.35, CHCl_3), as an inseparable 30:1 mixture¹² 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 ^1H NMR (500 MHz) spectrum. Treatment of **12** with a catalytic amount of PPTS in boiling ethanol followed by silica gel column chromatography¹³ gave the triol **13**,¹⁴ $[\alpha]_D^{22} -16.8^\circ$ (c 0.37, CHCl_3), in 41% yield. Finally, saponification of **13** with potassium hydroxide in aqueous methanol furnished (1*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, $[\alpha]_D^{22} -15.8^\circ$ (c 1.00, CHCl_3) [lit.^{3g} $[\alpha]_D^{20} -16.4^\circ$ (c 0.4, CHCl_3)], exhibited spectral properties (^1H 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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- 3 For the syntheses of **1** and related fatty acids, see: a) A. V. Rama Rao, P. R. Krishna, and J. S. Yadav, *Tetrahedron Lett.*, **30**, 1669 (1989); b) J. S. Yadav and M. C. Chander, *Tetrahedron Lett.*, **31**, 4349 (1990); c) P. Quinton and T. L. Gall, *Tetrahedron Lett.*, **32**, 4909 (1991); d) W.-L. Wu and Y.-L. Wu, *J. Chem. Soc., Perkin Trans.1*, **1992**, 2705; e) W.-L. Wu and Y.-L. Wu, *Tetrahedron Lett.*, **33**, 3887 (1992); f) W.-L. Wu and Y.-L. Wu, *J. Org. Chem.*, **58**, 2760 (1993); g) W.-L. Wu and Y.-L. Wu, *J. Chem. Soc., Perkin Trans.1*, **1993**, 3081; h) A. Baudat and P. Vogel, *Helv. Chim. Acta*, **77**, 1500 (1994).
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- 8 All new compounds reported herein exhibited satisfactory spectral (^1H NMR, IR, MS) and analytical (HR MS) data.
- 9 **6**: ^1H 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**: ^1H NMR (300 MHz, CDCl_3) δ 2.25 (1H, dt, $J=14.2$ and 7.7 Hz), 2.47 (1H, d, $J=4.3$ Hz), 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**: ^1H 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 ^1H NMR (300 MHz) analysis.
- 13 Other olefinic geometrical isomers were also obtained and not fully characterized.
- 14 **13**: ^1H 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.