Communications to the Editor

Chem. Pharm. Bull.
33(5)2168—2170(1985)

SYNTHESIS BY MICROBIAL REDUCTION OF (*S*)-13-HYDROXY-9*Z*,11*E*-OCTADECADIENOIC ACID, A DEFENSIVE SUBSTANCE IN RICE

Hiroshi Suemune,[a] Noriyuki Hayashi,[a] Kazuhisa Funakoshi,[a]
Hiroyuki Akita,[b] Takeshi Oishi,[b] and Kiyoshi Sakai*,[a]

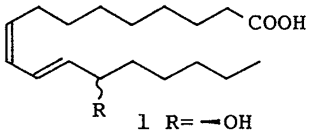
Faculty of Pharmaceutical Sciences, Kyushu University,[a]
Maidashi, Higashi-ku, Fukuoka 812, Japan and The Institute
of Physical and Chemical Research(Rikagaku Kenkyusho),[b]
Wako-shi, Saitama 351-01, Japan

(*S*)-13-Hydroxy-9*Z*,11*E*-octadecadienoic acid, a defensive substance in rice, was synthesized with high enantioselectivity by the reduction of the corresponding ketone with yeasts.

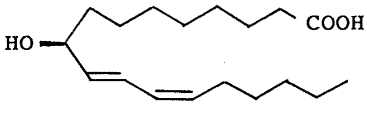
KEYWORDS —— asymmetric reduction; microbial reduction; hydroxy octadecadienoic acid; rice blast disease; ynenone

In 1966, Tallent[1] isolated (*R*)-13-hydroxy-9*Z*,11*E*-octadecadienoic acid (1, coliolic acid) and (*S*)-9-hydroxy-10*E*,12*Z*-octadecadienoic acid (3, dimorphecolic acid)[2] from the seed oil of *Coriolia nepalensis*. Isolation of 3 and (*S*)-13-hydroxy-9*Z*,11*E*-octadecadienoic acid (2) as defensive substances against rice blast disease in rice (*Oryza sative* L.) was also reported in 1984 by Kato.[3] A recent report of the synthesis of *dl*-1 and *dl*-3 by Rao[4] prompts us to describe the total synthesis of 2 based on microbial reduction.

Our strategy for the synthesis of 2 and 3 was as follows. i) The *cis* double bond and the *trans* double bond may be introduced by catalytic hydrogenation of the triple bond and Horner Wadsworth Emmons (HWE) reaction,[5] respectively. ii) The introduction of the chiral center in 2 and 3 may be accomplished by asymmetric reduction of the ketone with yeast.



1 R=—OH
2 R=····OH

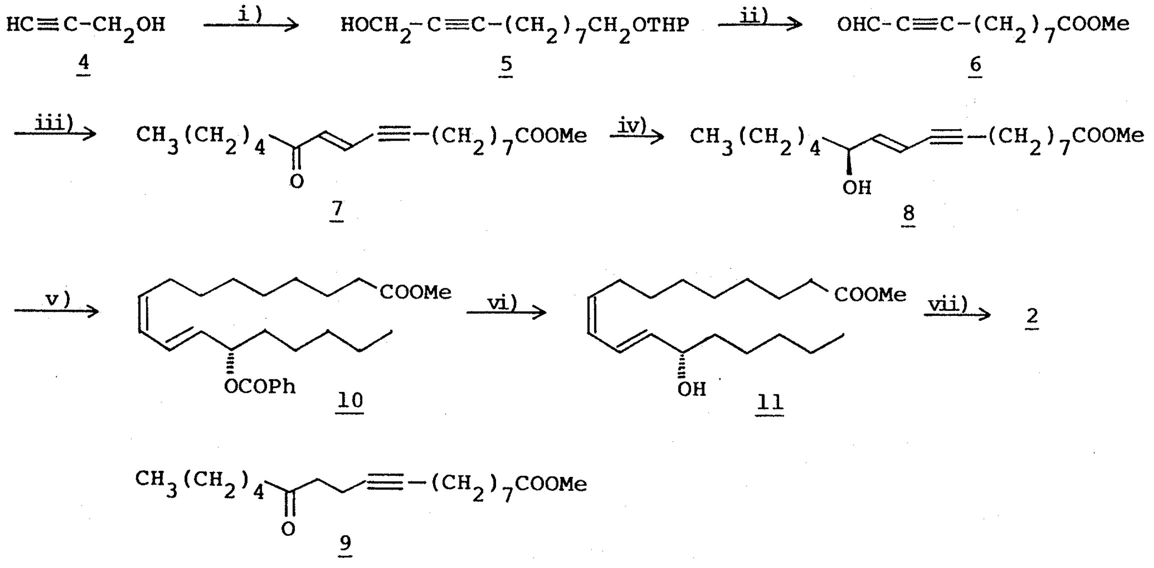


3

The synthetic intermediate, ynenone (7), was obtained in 30% overall yield from propargyl alcohol (4) as shown in Chart 1. In the asymmetric reduction of 7 using the microorganisms, the first screening was carried out with forty species of yeasts.[6] Among these, *Saccharomyces acidifaciens* and *Shizosaccharomyces octosporus* reduced the ketone function to afford the alcohol (**8**, $[\alpha]_D^{27}$ +8.8°(c=1.6, $CHCl_3$)) in 32% and 26% yield, respectively.[7] The ynone (**9**), in which the double bond rather than the ketone function was preferentially reduced, was also obtained with both yeasts. In the case of *Saccharomyces* *cerevisiae* (Baker's yeast), **9** was the major product (74%).

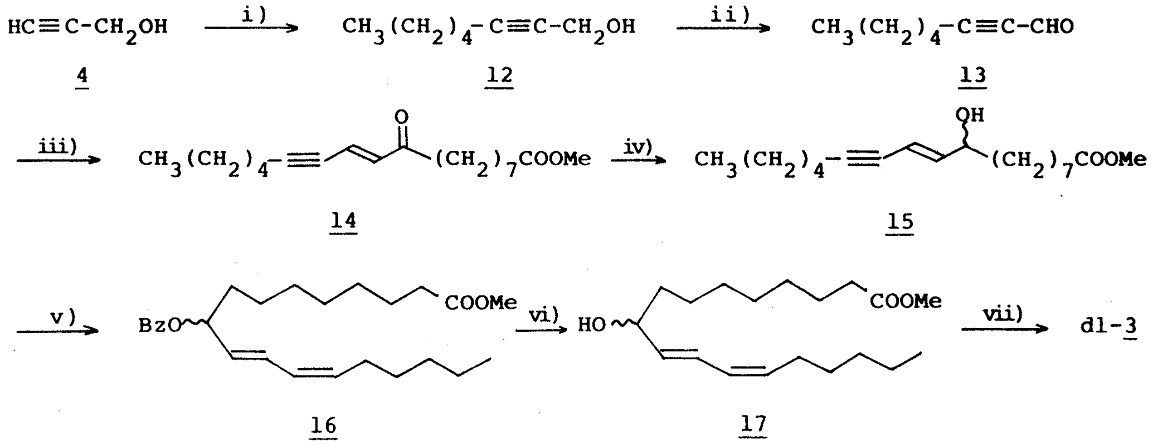
To estimate the optical purity, **8** was converted to the ester of (-)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA),8) and the optical purity was determined by direct comparison with the ^{1}H-NMR(400MHz) spectra of the (-)-MTPA ester of *dl*-**8**. The microbial reduction of the α,β-unsaturated ketone to allylic alcohol had been considered to be difficult,9) and only a few successful attempts were reported.10) There are no precedents to the microbial reduction of the ynenone function. It is noteworthy that the optical purity of the alcohol (**8**) was over 99% ee in both yeasts. After protection of the hydroxy group in **8** as the benzoate (92%), the triple bond was partialy hydrogenated, using the Lindlar catalyst in the presence of pyridine, to yield the *cis*,*trans*-diene (**10**)11) ($[\alpha]_D^{25}$+64.1°(c=1.5, $CHCl_3$)) in 79% yield. The ^{1}H-NMR spectrum of **10** was in good agreement with the reported value.3) **10** was converted into the target (**2**)12) via **11**13) in 70% yield.

In the synthesis of dimorphecolic acid (**3**), the ynenone ester (**14**) was synthesized in 48% overall yield from propargyl alcohol (**4**) as shown in Chart 2. Unlike **7**, the reduction of **14**, which has the same chromophore as **7**, with *Saccharomyces acidifaciens* and *Shizosaccharomyces octosporus* did not give the target (**15**). Reduction of **14** with $NaBH_4$ afforded *dl*-methyl helenynolate (**15**)14) in 95% yield. **15** was converted into *dl*-**3** via **16** and **17** in 72% yield.



i) $LiNH_2$, liq. NH_3, $Br(CH_2)_8OTHP$. ii) a) Ac_2O, pyridine; b) Jones oxd.; c) CH_2N_2; d) K_2CO_3, MeOH; e) PDC. iii) $CH_3(CH_2)_4COCH_2PO(OMe)_2$, DBU, LiCl. iv) reduction with yeasts. v) a) PhCOCl, pyridine; b) Lindlar cat./H_2, pyridine. vi) K_2CO_3, MeOH. vii) K_2CO_3, aq. MeOH.

Chart 1



i) $LiNH_2$, liq. NH_3, $CH_3(CH_2)_4Br$. ii) PCC. iii) $(MeO)_2POCH_2CO(CH_2)_7COOMe$, DBU, LiCl. iv) $NaBH_4$. v) a) PhCOCl, pyridine; b) Lindlar cat./H_2, pyridine. vi) K_2CO_3, MeOH. vii) K_2CO_3, aq. MeOH.

Chart 2

REFERENCES AND NOTES

1) a) W.H.Tallent, J.Harris, I.A.Wolff, Tetrahedron Lett., **1966**, 4329; b) H.B. S.Conacher, F.D.Gunstone, Chem. Commun., **1968**, 281.
2) R.C.Badami, L.J.Worris, J. Am. Oil Chem. Soc., **42**, 1119(1965).
3) T.Kato, Y.Yamaguchi, T.Hirano, T.Yokoyama, T.Uyehara, T.Namai, S.Yamanaka, N.Harada, Chem. Lett., **1984**, 409.
4) A.V.R.Rao, E.R.Reddy, G.V.M.Sharma, P.Yadagiri, J.S.Yadav, Tetrahedron Lett., **26**, 465(1985).
5) M.A.Blanchette, W.Choy, J.J.Davis, A.P.Essenfeld, S.Masamune, W.R.Roush, T.Sakai, Tetrahedron Lett., **25**, 2183(1984).
6) K.Horikoshi, A.Furuichi, H.Koshiji, H.Akita, T.Oishi, Agric. Biol. Chem., **47**, 435(1983).
7) The product was purified by silica gel column chromatography after treatment with CH_2N_2, because partial hydrolysis of the ester function was observed.
8) a)J.A.Dale, H.S.Mosher, J. Am. Chem. Soc., **95**, 512(1973); b) H.Akita, A. Furuichi, H.Koshiji, K.Horikoshi, T.Oishi, Tetrahedron Lett., **23**, 4051(1982).
9) C.J.Sih, J.P.Rosazza,''Application of Biochemical Systems in Organic Chemistry,''Part 4, John Wiley and Sons Inc., New York, p.75(1976).
10) a) M.Miyano, C.R.Dorn, F.B.Colton, J. Chem. Soc., Chem. Commun., **1971**, 425; b) C.J.Sih, J.B.Heather, R.Sood, P.Price, G.Peruzzotti, L.F.Hsu Lee, S.S. Lee, J. Am. Chem. Soc., **97**, 865(1975).
11) Kato reported the specific rotation of **10**($[\alpha]_D^{20}$+5.8°(c=1.3, $CHCl_3$)), which was derived from naturally occurring **2**, and decided the absolute chemistry to be (S)-configuration based on its positive CD curve. The much differnce in the specific rotation ($[\alpha]_D^{20}$+5.8° and $[\alpha]_D^{25}$+64.1°) suggests that **2** from rice consists of a partly racemic mixture, as Kato noted.[3)]
12) **2**: $[\alpha]_D^{23}$+7.8°(c=1.15, $CHCl_3$); ^1H-NMR($CDCl_3$) δ: 4.18(1H, m, C_{13}-H), 5.43(1H, dt, J=11.0, 8.0Hz, C_9-H), 5.66(1H, dd, J=15.5, 7.0Hz, C_{12}-H), 5.97(1H, dd, J=11.0, 11.0Hz, C_{10}-H), 6.49(1H, dd, J=15.5, 11.0Hz, C_{11}-H). MS m/z: 296 (M^+), 278.
13) **11**: $[\alpha]_D^{24}$+6.0°(c=1.6, hexane). Methyl ester of **1** (reported value)[1a)]: $[\alpha]_D^{23}$ -7.5°(c=2.3, hexane).
14) a) R.G.Powell, C.R.Smith,Jr., C.A.Glass, I.A.Wolff, J. Org. Chem., **30**, 610 (1965); b) T.B.Patric, G.F.Melm, J. Org. Chem., **44**, 645(1979).

(Received March 18, 1985)