Total Synthesis of α-Ketol Derivative of Linolenic Acid (KODA), a Flower-inducing Factor in *Lemna paucicostata*

Yoshihiro Yokokawa,* Kouji Kobayashi, Mineyuki Yokoyama, and Shosuke Yamamura†
Material Science Research Center, Shiseido Co. Ltd., Yokohama 224-8558
†*Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223-8522*

(Received June 16, 2003; CL-030539)

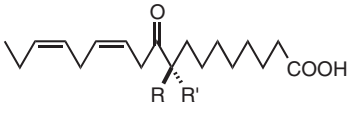
Racemic 9-hydroxy-10-oxo-12(*Z*),15(*Z*)-octadecadienoic acid [(±)-KODA] was synthesized via a coupling reaction between a diyne and an epoxide derived from methyl oleate as a key step. An optically active 9*R*-KODA was also synthesized by enantioselective lipase-catalyzed esterification of an allyl alcohol. Both synthetic (±)-KODA and 9*R*-KODA showed remarkable flower-inducing activity in *Pharbitis nil*.

α-Ketol derivative of linolenic acid [KODA, **1**] was isolated as an essential component of factor C, which showed potent flower-inducing activity in *Lemna paucicostata* upon incubation with norepinephrine (NE).[1] The absolute structure of KODA was found to be predominantly 9*R* (70% 9*R* and 30% 9*S*),[2] as shown in Figure 1. As an extension of our studies on flower-inducing activity of KODA, 9*R*-11-{(2′*S*,8′*S*,10′*S*,11′*R*)-2′,8′-dihydroxy-7′-oxo-11′-[(*Z*)-2-pentenyl]-9′-oxa-4′-azatricyclo[6.3.1.0^{1,5}]dodec-5′-en-10′-yl}-9-hydroxy-10-oxoundecanoic acid (FN1, **2**) was isolated with FN2 (**3**), the C-9 epimer of FN1, as two major components of the incubated mixture of KODA with NE (Figure 1). Flower-inducing activity was observed in only FN1, which was derived from 9*R*-KODA (**1a**), not in FN2.[2] More recent studies have suggested that KODA may be involved in flower induction in *Pharbitis nil* (violet) with the evident relation between KODA concentration and the flower-inductive condition.[3] In this communication, we report a total synthesis of (±)-KODA (**1**) by using a coupling reaction between a diyne and an epoxide as a key step, and an enantioselective synthesis of 9*R*-KODA (**1a**) via enantioselective lipase-catalyzed esterification of an allyl alcohol **6**.[4] In addition, the synthetic KODA remarkably promoted flower induction in *Pharbitis nil*. This is the first result that showed flower-inducing activity of KODA in other plants besides *L. paucicostata*.

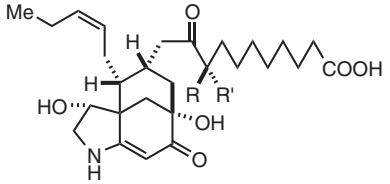
Ozonolysis of methyl oleate (**4**) in MeOH–CH_2Cl_2 (1:1) at −17 °C with Me_2S as a reducing agent afforded **5**,[5] which was submitted to a Grignard reaction with vinylmagnesium bromide in THF at −25 °C to give an allyl alcohol **6**, as shown in Scheme 1. Treatment of **6** with MCPBA in CH_2Cl_2 containing sat. aq $NaHCO_3$ afforded an epoxide **7**, and subsequent protection of **7** with *tert*-butyldimethylsilyl chloride in DMF in the presence of imidazole yielded **8** which was subjected to a coupling reaction.[6] Namely, treatment of **8** with 1,4-heptadiyne (**9**)[7] and *n*-BuLi in THF in the presence of $BF_3{\cdot}Et_2O$ at −50 °C afforded a coupling product **10** in 87.6% yield. Selective hydrogenation of **10** with Lindlar's catalyst (10%) in toluene afforded **11** and subsequent Swern oxidation furnished a ketone **12**.[8] Deprotection of the TBDMS group in **12** with 46% aq HF–H_2O yielded **13**. Finally, enzymatic removal of the methyl group in **13** with lipase PS in a solution of 0.1 M phosphate buffer (pH 7.0) and acetone (1:1) afforded (±)-KODA (**1**),[9] in 2.35% overall yield[10] from methyl oleate (**4**), which was identified with an authentic sample by TLC, HPLC, MS, IR, and ^{1}H NMR (CD_3OD).

To synthesize 9*R*-KODA (**1a**), an allyl alcohol **6** was subjected to lipase-catalyzed enantioselective acetylation. Namely, treatment of **6** with lipase PS (50 g/mol of **6**) and vinyl acetate (5 equiv.) in pentane at 30 °C yielded an acetylated product **14** with (−)-**6**[11] as the recovered substrate. The configuration of C-9 in (−)-**6** was found to be *R* with 99% ee by utilizing a modified Mosher method[12] on the MTPA esters of (−)-**6**. According to a similar procedure from **6** to (±)-KODA (**1**), 9*R*-KODA (**1a**)[13] was synthesized from (−)-**6** in a total yield of 0.81% from **4**.

We examined the flower-inducing activity of (±)-KODA (**1**) and 9*R*-KODA (**1a**) on *P. nil* (violet), which is a typical short-day plant. Its flowering process is so sensitive that flowering is induced by exposing a seedling cultivated under continuous light in a single 16 h dark period.[14] In a restricted condition (14 h dark period) in which control (water spray) induced one flower in average, (±)-KODA (**1**) and 9*R*-KODA (**1a**) at 100 μM promoted the flower induction in 129% and 215%, respectively.[15] The activity of chemically synthesized KODA was estimated to be equivalent to that of KODA which was prepared in enzymatic process.[2] Based on this evidence, the absolute configuration at the 9-position has an important role for the activity in addition to the diene and α-ketol moiety[1] in **1**. This result also suggested that KODA might have flower-inducing activity in various kinds of plants as a hormone.

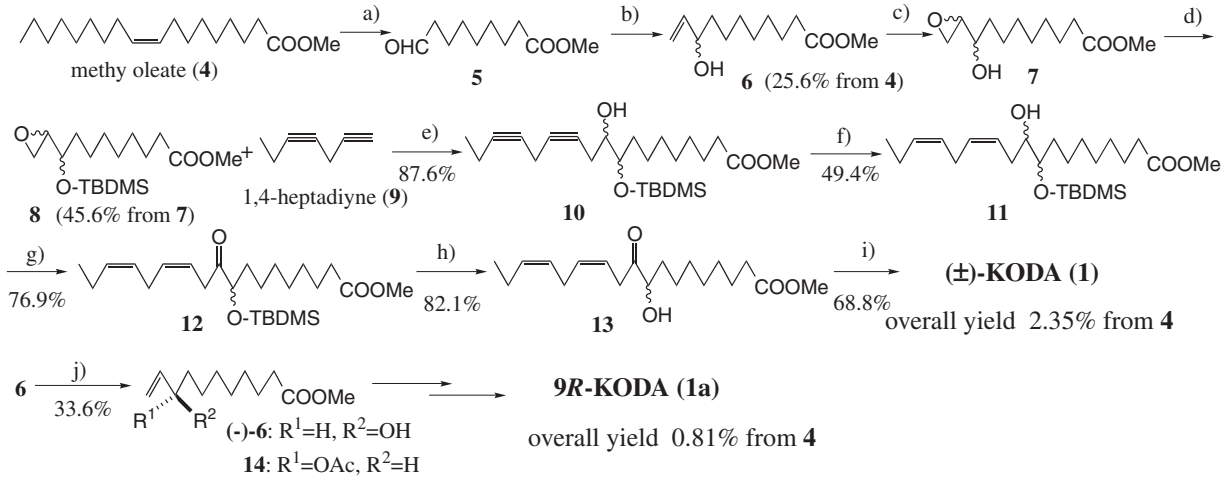


9*R*-KODA (**1a**) : R=OH, R'=H
9*S*-KODA (**1b**) : R=H, R'=OH



FN1 (**2**) : R=OH, R'=H
FN2 (**3**) : R=H, R'=OH

Figure 1. Structures of flower-inducing factor.



Scheme 1. Synthesis of (±)-KODA and 9*R*-KODA Reagents and conditions: a) O_3/MeOH, then Me_2S; b) vinylmagnesium bromide/THF; c) MCPBA/CH_2Cl_2-sat. aq $NaHCO_3$; d) TBDMS-Cl/imidazole/DMF; e) BF_3-Et_2O/*n*-BuLi/THF; f) H_2, Lindlar's cat. (10%)/toluene; g) Swern oxid.; h) 46% aq HF-CH_3CN; i) lipase PS/0.1 M phosphate buffer (pH7)-acetone (1:1); j) lipase PS/vinyl acetate/pentane.

References and Notes

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5 All new compounds were characterized by physicochemical properties. The structures of the compounds (**7**, **8**, **10**, **11**) were supported by their spectral data, even though they were diastereomeric mixtures.

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8 **12**, colorless oil, $[\alpha]_D^{26}$ +13.1° ($CHCl_3$), $C_{25}H_{46}O_4Si$, IR (film): 3020, 2953, 2932, 2858, 1731, 1255, 1216, 758 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.03(3H, s), 0.04(3H, s), 0.91(9H, s), 0.95(3H, t, $J = 7.5$ Hz), 1.26–1.56(12H), 2.04(2H, m), 2.27(2H, t, $J = 7.5$ Hz), 2.74(2H, t, $J = 6.0$ Hz), 3.34(2H, dd, $J = 5.0$, 7.0 Hz), 3.64(3H, s), 4.03(1H, dd, $J = 5.5$, 7.5 Hz), 5.28(1H, m), 5.38(1H, m), 5.56(2H, m).

9 **1**, colorless oil, $C_{18}H_{30}O_4$, IR (film): 3420, 3020, 2936, 2860, 1710, 1216, 766 cm^{-1}. ^1H NMR (CD_3OD) δ: 0.97(3H, t, $J = 7.5$ Hz), 1.28–1.71(12H), 2.08(2H, m), 2.26(2H, t, $J = 7.5$ Hz), 2.79(2H, m), 3.35(2H, t, $J = 5.0$ Hz), 4.10 (1H, m), 5.29 (1H, m), 5.40 (1H, m), 5.54 (2H, m).

10 Each reaction condition has not been optimized.

11 (−)-**6**, colorless oil, $[\alpha]_D^{26}$ −3.41° ($CHCl_3$), $C_{12}H_{22}O_3$, IR (film): 3448, 3079, 2932, 2856, 1740, 1437, 1172 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.27–1.57 (12H), 2.26 (2H, t, $J = 7.5$ Hz), 3.62 (3H, s), 4.04 (1H, m), 5.05 (1H, d, $J = 10.0$ Hz), 5.17 (1H, dd, $J = 1.5$, 10.0 Hz), 5.82 (1H, m).

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13 **1a**, colorless oil, $[\alpha]_D^{26}$ −14.7° (MeOH), $C_{18}H_{30}O_4$, IR and ^1H NMR data were identical to those of **1**.

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15 The detailed activity will be presented elsewhere.

Published on the web (Advance View) August 11, 2003; DOI 10.1246/cl.2003.844