A Convenient Synthesis of (±)-Dimorphecolic Acid and Its Analogs

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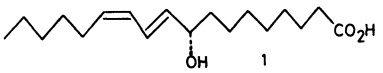
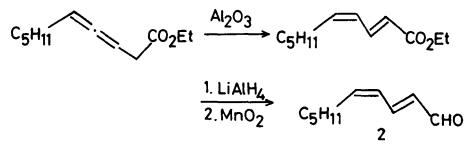
Synopsis. Dimorphecolic acid, self-defensive substances in rice plant against rice blast disease, and its analogs were prepared stereoselectively by the reaction of (2*E*,4*Z*)-2,4-decadienal with Grignard reagents.

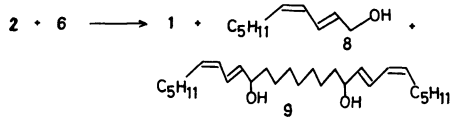
Dimorphecolic acid (**1**) is one of self-defensive substances in rice plant against rice blast disease, which were isolated by Kato et al.[1] Compound **1** is also found in oil of vegetables and is shown to possess a unique ionophore activity.[2] Recently Morota et al. reported that dimorphecolic acid isolated from Lycium chinese Mill acts as an inhibitor against angiotensin I converting enzyme (ACE), namely as a hypotensive substance.[3] Rao et al. reported the first synthesis of **1** via several steps from epichlorohydrin.[4]

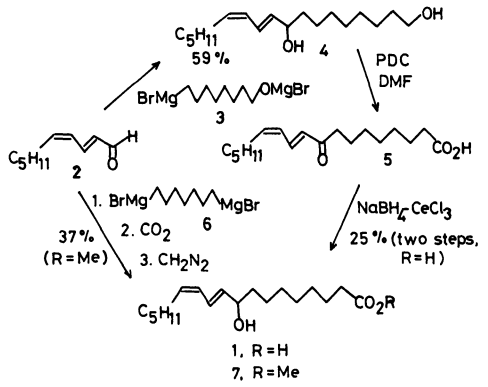


We present here a convenient synthesis of **1** via (2*E*,4*Z*)-2,4-decadienal. The synthetic sequence is shown in Scheme 1. The starting material, (2*E*,4*Z*)-2,4-decadienal (**2**) can be obtained by the reduction of ethyl (2*E*,4*Z*)-2,4-decadienoate, which was prepared by the stereoselective rearrangement of ethyl 3,4-decadienoate promoted with alumina, and the subsequent oxidation of the product.[5]



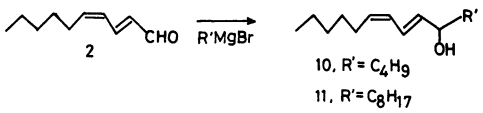
Reaction of **2** with Grignard reagent **3**[6] from 8-chloro-1-octanol gave the diol **4** in 59% yield. Oxidation of **4** with pyridinium dichromate in *N*,*N*-dimethylformamide (DMF) gave the keto acid **5**.[7] Reduction of **5** with $NaBH_4$–$CeCl_3$ in methanol afforded dimorphecolic acid (25% yield from **4**). On the other hand, one-pot synthesis of **1** was established by the reaction of **2** with 1,7-heptanediyldimagnesium dibromide (**6**)[8] followed by carboxylation and esterification (37% total yield as the methyl ester **7**). The ester **7** was converted to the benzoate, of which ^{13}C NMR data were identical with those of the literature.[1a] This carboxylation was accompanied by the formation of (2*E*,4*Z*)-2,4-decadien-1-ol (**8**) (15%) and tetraenediol **9** (42%), the reaction product of **6** with two equivalents of **2**. These compounds could be separated by HPLC or medium pressure chromatography. The present synthesis is one of rare examples[8d] of the application of di-Grignard reagents for the synthesis of natural products.





Scheme 1.

Furthermore, analogs of **1** were prepared in good yields by the reaction of **2** with Grignard reagents such as butylmagnesium bromide and octylmagnesium bromide as shown below. The biological activity of dienols **10** and **11** was examined against rice plant diseases. Neither **10** nor **11** showed any control activities against diseases such as rice blast, rice sheath blight, and rice brown spot. This fact shows clearly that a carboxyl group of **1** plays an important role for biological activity.



Although the present synthesis does not afford a high yield of **1**, the simplicity makes it more attractive than the previously reported ones.[4]

Experimental

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Eiichiro Amano in our laboratory. Infrared (IR) spectra were obtained with a JASCO Model A-102 infrared spectrophotometer. High-performance liquid chromatography (HPLC) was performed with Hitachi Model 655 liquid chromatograph and Shodex Model SE-31 differential refractometer. ^1H NMR spectra (60 MHz) were recorded with a JEOL JNM-PMX60SI apparatus. ^{13}C NMR spectra were obtained with a JEOL JNM-FX100 apparatus, in $CDCl_3$ solvent. All chemical shifts are reported in δ units downfield from internal Me_4Si, and J values are given in herz. Column chromatography was accomplished with 100—200 mesh Wakogel C-200. Aldehyde **2** was prepared by the procedures described in the previous paper[5] and purified by column chromatography [silica gel, hexane–ethyl acetate (20:1—10:1)]. The purity (>95%) was checked by ^1H NMR spectrum.

(10*E*,12*Z*)-10,12-Octadecadiene-1,9-diol (4). To a mix-

ture of 73.6 mg (3.03 mg-atom) of magnesium and 0.5 ml of THF was added dropwise 0.115 ml (168 mg, 1.54 mmol) of ethyl bromide and the mixture was stirred for 1.5 h. After the dropwise addition of a solution of 8-bromo-1-octanol (316 mg, 1.51 mmol) in THF (1 ml) at 0 °C, the mixture was stirred for 30 min at 0 °C and then for 2.5 h at room temperature. At this interval 2—3 ml of THF was added. To the stirred mixture was added dropwise a solution of 152 mg (1 mmol) of **2** in 1 ml of THF at 0 °C. After the addition, the ice bath was removed and the mixture was stirred for 1.5 h. The reaction mixture was poured into aqueous NH_4Cl and extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, and concentrated, and the resulting residue (410 mg) was chromatographed on 17 g of silica gel eluting with hexane–ethyl acetate–methanol (45:3:1) to give 149 mg (59%) of **4**: IR (neat) 3320 (OH), 2930, 1460, 1120, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 (3H, t, J=6 Hz, CH_3), 1.33 (20H, br. S, $CH_3(CH_2)_3$, $(CH_2)_7CH_2OH$), 1.88 (2H, S, 2OH), 2.11 (2H, t, J=7 Hz, CH_2CH=CH), 3.58 (2H, t, J=6 Hz, CH_2OH), 4.15 (1H, m, $\geq$CHOH), 5.2—6.2 (3H, m, CH=CHCH=CHCHOH-), and 6.50 (1H, dd, J=10 and 15 Hz, CH=CHCHOH-). Found: C, 76.37; H, 12.27%. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13%.

Oxidation of 4 with Pyridinium Dichromate. To a solution of 1.28 g (3.40 mmol) of pyridinium dichromate[9] in 1 ml of DMF was added a solution of 160 mg (0.566 mmol) of **4** in 1.5 ml of DMF at 0 °C under an atmosphere of nitrogen. The mixture was stirred for 14 h at room temperature and then poured into water. The organic layer was extracted with ether, washed with water, dried over $MgSO_4$, and concentrated to give 124 mg of crude **5**: IR (neat) 3600—2500 (CO_2H), 1710 (C=O), 1590, 1460, and 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (3H, t, J=7 Hz, CH_3), 1.25 (16H, br. S, $CH_3(CH_2)_3$, $(CH_2)_5CH_2CO_2H$), 2.33 (4H, m, CH_2CH=CH, CH_2CO_2H), 3.38 (2H, t, J=5.5 Hz, CH_2COCH=), 5.5—6.4 (3H, m, CH=CHCH=CHCO), and 7.50 (1H, dd, J=10.5 and 16 Hz, CH=CHCO). The crude **5** was used for next step without purifucation.

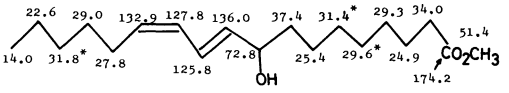
Dimorphecolic Acid (1). To a solution of 313 mg (0.84 mmol) of cerium(III) chloride in 10 ml of methanol was added a solution of 124 mg (0.421 mmol) of **5** in 5 ml of methanol. Sodium borohydride (31.9 mg, 0.843 mmol) was added in several portions at 0 °C and the mixture was stirred for 4 h at 30—35 °C, and then poured into ice water, acidified with dilute HCl, and extracted with ether. The ethereal solution was washed with water, dried over $MgSO_4$, concentrated, and chromatographed on 7 g of silica gel eluting with hexane–ethyl acetate–methanol (45:4:1) to give 40.6 mg (25% yield estimated from **4**) of **1**:[1a] IR (neat) 3300—2500 (CO_2H), 1710 (C=O), 1460, 1410, and 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 (3H, t, J=6 Hz, CH_3), 1.28 (18H, m, $CH_3(CH_2)_3$, $(CH_2)_6CH_2CO_2H$), 2.0—2.5 (4H, m, CH_2CH=CH, CH_2CO_2H), 4.1 (1H, m, $\geq$CHOH), and 5.2—7.2 (5H, m, $\{CH=CH\}_2$, CO_2H).

Methyl Dimorphecolate (7) and (6*Z*,8*E*,19*E*,21*Z*)-6,8,19,21-Heptacosatetraene-10,18-diol (9). To a mixture of 53.7 mg (2.21 mmol) of magnesium and 1 ml of THF was added dropwise a solution of 0.17 ml (257 mg, 0.996 mmol) of 1,7-dibromoheptane in 1 ml of THF at 30—35 °C over 3 h. The mixture was stirred for 1 h and then 0.18 ml (175 mg, 0.98 mmol) of hexamethylphosphoric triamide (HMPA) was added at 15—18 °C. After 30 min, a solution of 120 mg (0.788 mmol) of **2** in 1.5 ml of THF was added dropwise, and the mixture was stirred for 1.5 h and then cooled at 0 °C. Carbon dioxide dried over anhydrous magnesium perchlorate was introduced and the mixture was stirred for 3 h under an atmosphere of carbon dioxide, and then poured into aqueous NH_4Cl cooled with ice. The mixture was acidified with dilute HCl and extracted three times with ether. The ethereal solution was washed with brine, dried ($MgSO_4$), and concentrated to give 286 mg of an oil, which was treated with diazomethane in ether. After concentration, the residual oil (288 mg) was analyzed by HPLC [column, SA-I (7.5 mmϕ×25 cm); elution, hexane–ethyl acetate–acetonitrile (10:3:1), 1 ml min^{-1}]. Peaks, retention times (min), integrated percentages are as follows: 1, 6.29, 9.9%; 2, 7.78, 45.5%; 3, 8.97, 31.7%; 4, 11.4, 12.9%. Each component was separated by preparative HPLC and assigned by spectral data.

Peak 1: 1,7-dibromoheptane.

Peak 2: **9**; 41% yield; IR (neat) 3350 (OH), 2950, 1462, and 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (6H, t, J=6 Hz, $2CH_3$), 1.35 (26H, br. s, $2CH_3(CH_2)_3$, $(CH_2)_7CHOH$), 1.78 (2H, s, 2OH), 1.9—2.4 (4H, m, $2CH_2CH$=CH), 4.02 (2H, m, 2 $\geq$CHOH), 5.00—6.09 (6H, m, 2CH=CHCH=CHCHOH-), 6.32 (2H, dd, J=10 and 15 Hz, 2CH=CHCHOH-). Found: C, 80.37; H, 11.74%. Calcd for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96%.

Peak 3: **7**;[1a] 37% yield; IR (neat) 3450 (OH), 2940, 1745 (CO_2CH_3), 1460, 1435, 1195, 1170, and 981 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (3H, t, J=5 Hz, CH_3), 1.35 (18H, br s, $CH_3(CH_2)_3$, $(CH_2)_6CH_2CO_2CH_3$), 1.9—2.4 (4H, m, CH_2CH=CH, $CH_2CO_2CH_3$), 3.57 (3H, s, CO_2CH_3), 4.02 (1H, m, $\geq$CHOH), 5.03—6.06 (3H, m, CH=CHCH=CHCHOH-), and 6.35 (1H, dd, J=10 and 15 Hz, CH=CHCHOH). ^{13}C NMR data ($CDCl_3$, δ) were tentatively assigned.[10]



Found: C, 73.31; H, 10.80%. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04%.

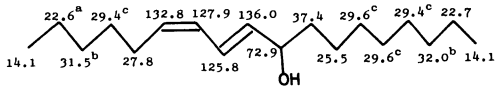
Peak 4: **8**; IR and ^1H NMR spectra were identical with those of the literature.[5]

Methyl (10*E*,12*Z*)-9-benzoyloxy-10,12-octadecadienoate was prepared in 69% yield by the treatment of **7** (23 mg, 0.0744 mmol) with benzoyl chloride (13.2 mg, 0.0941 mmol) in pyridine (0.1 ml) at 20—25 °C for 5 h. Its ^{13}C NMR data was identical with those of the literature.[1a]

(6*E*,8*Z*)-6,8-Tetradecadien-5-ol (10). To a mixture of 162 mg (6.67 mmol) of magnesium in 0.5 ml of THF was added dropwise a solution of 0.59 ml (750 mg, 5.47 mmol) of butyl bromide in 1 ml of THF, occasionally cooling with water. After 2 h, a solution of 854 mg (5.47 mmol) of **2** in 1.5 ml of THF was added dropwise at 0 °C, and then the mixture was stirred for 30 min at 0 °C. After an additional stirring for 1 h at room temperature, the mixture was poured into aqueous NH_4Cl and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give 1.21 g of crude **10**. Preparative TLC gave 0.988 g (86%) of pure **10**: IR (neat) 3370 (OH), 2950, 1460, 1375, 980, and 950 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (6H, t, J=5 Hz, $2CH_3$), 1.36 (12H, br. s, $2CH_3(CH_2)_3$), 1.8—2.5 (3H, m, CH_2CH=, OH), 4.05 (1H, m, $\geq$CHOH), 5.28 (1H, m, CH=CHCH=CHCHOH-), 5.58 (1H, m, CH=CHCHOH-), 5.86 (1H, t, J=10 Hz, CH=CHCH=CHCHOH-), and 6.39 (1H, dd, J=10 and 15 Hz, CH=CHCHOH-). Found: C, 79.74; H, 12.62%. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46%.

(10*E*,12*Z*)-10,12-Octadecadien-9-ol (11). A solution of 850 mg (5.58 mmol) of **2** in 1.5 ml of THF was treated with a THF solution of octylmagnesium bromide prepared from magnesium (162 mg, 6.67 mmol), 1-bromooctane (1.33 g, 6.99 mmol) and THF (1 ml), as shown in the preparation of **10**. The reaction mixture was worked up as usual to give 1.63 g of crude **11**, which was purified by preparative TLC (silica gel, hexane–ethyl acetate (2:1)) to give 1.29 g (87%) of pure **11**: IR (neat) 3370 (OH), 2950, 1460, 1380, and 980 cm^{-1}; ^1H NMR (CCl_4) δ=0.89 (6H, t, J=5.5 Hz, $2CH_3$), 1.28 (2OH, br. s, $CH_3(CH_2)_3$, $CH_3(CH_2)_7$), 1.95—2.41 (2H, m, CH_2CH=CH),

4.01 (1H, m, >CHOH), 5.26 (1H, m, CH=CHCH=CHCHOH), 5.53 (1H, m, CH=CHCHOH), 5.82 (1H, t, J=10 Hz, CH=CH CH=CHCHOH), and 6.35 (1H, dd, J=10 and 15 Hz, CH= CHCHOH-). ^{13}C NMR data ($CDCl_3$, δ).[10] Assignments of



a, b, c may be interchangeable. Found: C, 81.38; H, 12.72%. Calcd for $C_{18}H_{34}O$: C, 81.13; H, 12.86%.

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*Assignments may be interchangeable.