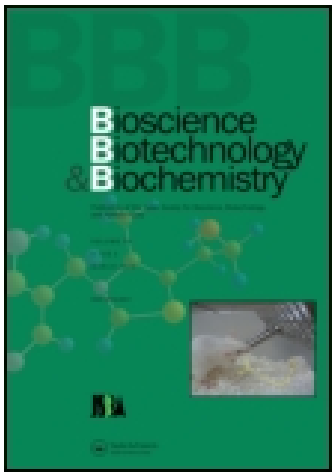

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Synthesis and Biological Activity of LL-P880γ and Its Analogues

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Note

Synthesis and Biological Activity of LL-P880γ and Its Analogues

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Stereoisomers and analogues of LL-P880γ (2) were synthesized and tested to elucidate its structure–activity relationship. Their evaluation in the gibberellin-synergistic assay with rice seedlings revealed a clear dependence of potency on the stereochemistry at C1′ on the side chain of 2.

Key words: LL-P880γ synthesis; pestalotin analogues; gibberellin synergist; GA synergistic activity on rice seedlings; *Penicillium* species metabolite

Fungal metabolites (6*S*,1′*S*)-LL-P880α (pestalotin, **1**), (6*S*, 1′*S*,2′*R*)-LL-P880β (**2a**) and (1′*S*,2′*R*)-LL-P880γ (**3a**) were co-produced by an unidentified *Penicillium* species.[1] Among these compounds, **1** and **3a** are potent gibberellin-synergists on rice seedlings, whereas **2a** hardly shows any synergistic activity.[2,3] Although the structure–activity relationship of pestalotin (**1**) and its related compounds has been elucidated by Kimura *et al.*,[3] there has been no report on the structure–activity relationship of LL-P880γ. In this report, we describe the preparation of stereoisomers and analogues of LL-P880γ, and also describe their biological evaluation.

Three stereoisomers (**3a–c**) of LL-P880γ, including a natural one, were synthesized from corresponding LL-P880β (**2a–c**)[3–5] without any racemization at the chiral centers according to our previous method,[4] in which the 2-pyrone ring of **3** was formed by the regio-selective bromination of protected **2** and subsequent

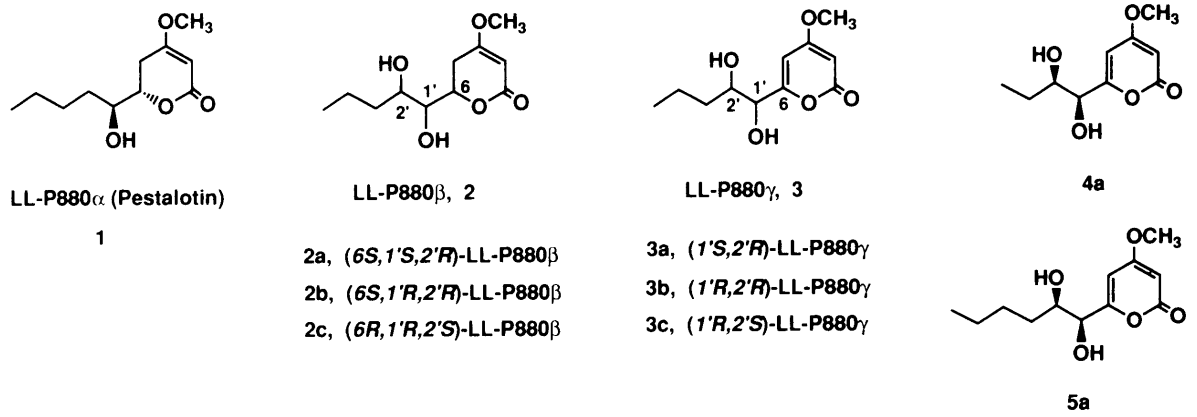
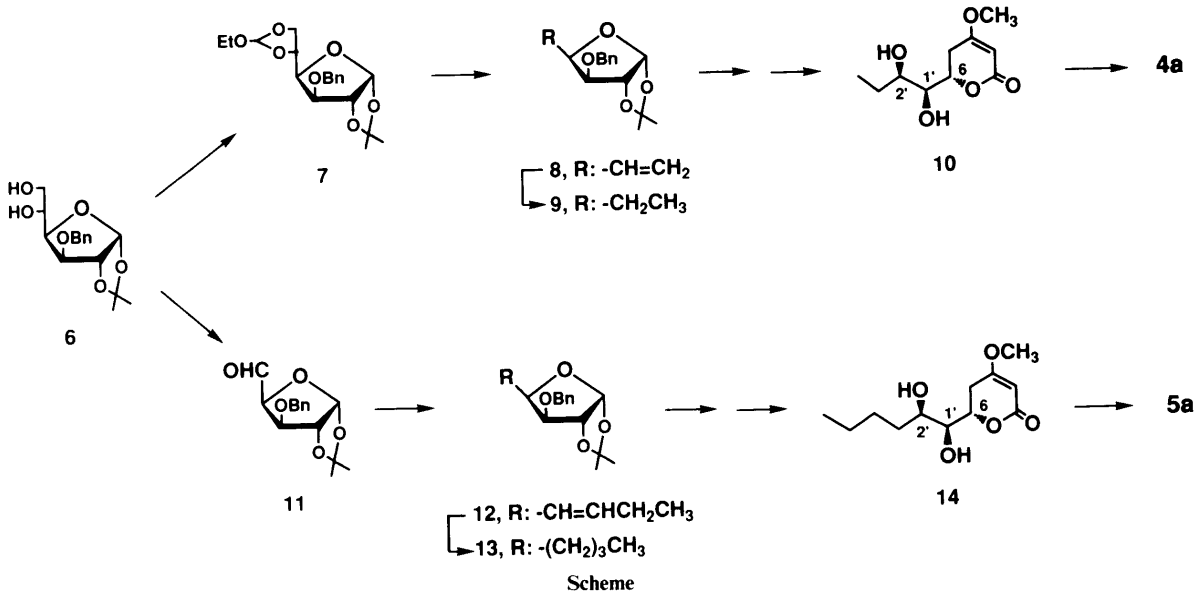


Fig. 1.



Scheme

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Abbreviation: GA_3, gibberellin A_3.

dehydrobromination.

In order to evaluate the effect of the *n*-propyl group at C2′ of **3a** on the biological activity, two novel analogues (**4a** and **5a**), which only differed from **3a** in their alkyl-chain length at C2′ were synthesized from the common starting material (**6**) *via* the corresponding LL-P880β analogues (**10** and **14**) as outlined in Scheme 1. Thus, the 5-deoxy-5-*C*-alkyl-α-D-xylofuranose derivatives (**9** and **13**) required as key intermediates for the syntheses of **10** and **14** were prepared from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**). In the upper route, cyclic orthoformation of **6** and subsequent pyrolysis gave olefin **8**,[7] which was then catalytically hydrogenated to furnish **9** in an 82% overall yield from **6**. On the other hand, a Wittig reaction of **11** and subsequent hydrogenation to elongate the three-carbon unit gave **13** in a 32% overall yield from **6**.

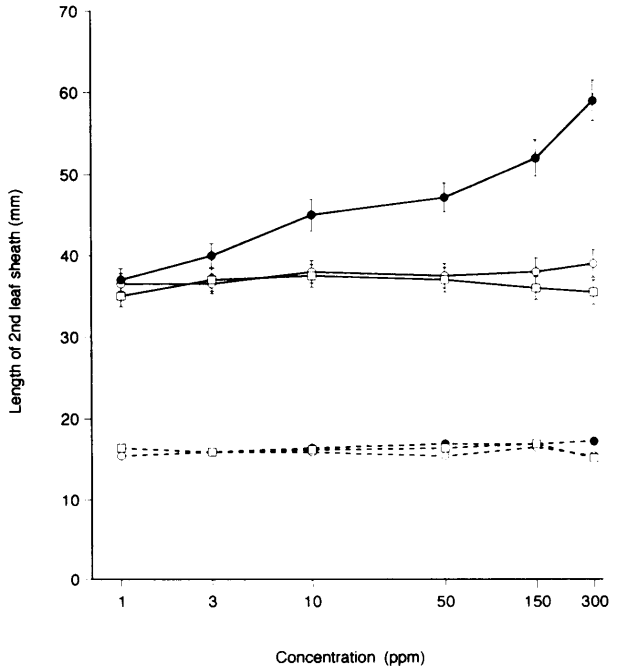

Fig. 2. Effect of Stereoisomers of LL-P880γ on Rice Seedlings in the Presence or Absence of GA_3.

Control length of second leaf sheath with GA_3 (1 mg/liter): 36±1.4 mm. Control length of second leaf sheath without GA_3: 15±0.4 mm. ●—●, **3a**+GA_3; ○—○, **3b**+GA_3; □—□, **3c**+GA_3; ●---●, **3a**; ○---○, **3b**; □---□, **3c**.

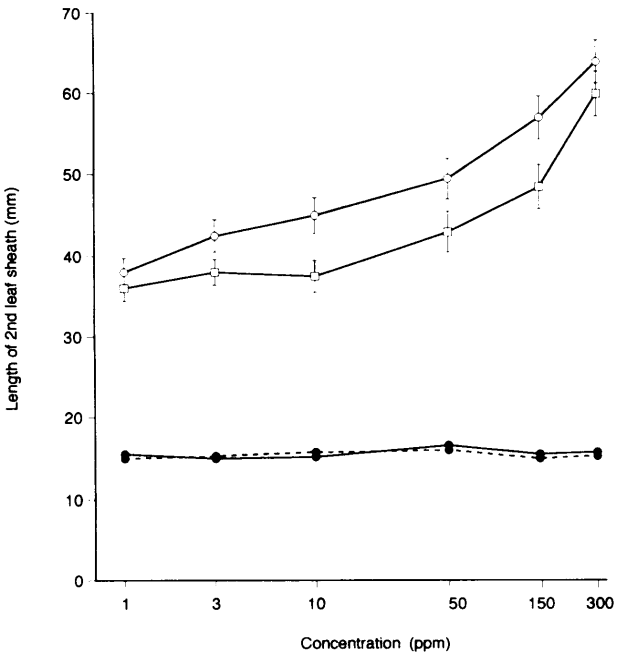

Fig. 3. Effect of Analogues of LL-P880γ on Rice Seedlings in the Presence or Absence of GA_3.

The control lengths are the same as those given in Fig. 2. ■—■, **4a**+GA_3; △—△, **5a**+GA_3; ■---■, **4a**; △---△, **5a**.

The sequence from key intermediate **9** to **10** could be carried out in a 9% overall yield by the known route, and the subsequent conversion of **10** into **4a** was accomplished in a 19% yield.[4] Similarly, **5a** was prepared from **13** *via* **14** in a 4% overall yield.

The gibberellin synergistic activity of these stereoisomers and analogues just synthesized was examined by using dwarf rice (*Oryzae sativa* L., c.v. *Tan-ginbozu*) according to the literature method.[3] As shown in Fig. 2, (1′*S*,2′*R*)-LL-P880γ (**3a**) alone at a dosage of 1–300 mg/liter did not affect the growth of the rice seedlings. However, when applied together with gibberellin A_3 (GA_3) at 1 mg/liter, **3a** enhanced the stimulative effect of GA_3 on the elongation of the second leaf sheath. In contrast, (1′*R*,2*R*)-LL-P880γ (**3b**) and (1′*R*,2′*S*)-LL-P880γ (**3c**) hardly showed any synergistic activity. Two analogues (**4a** and **5a**), whose alkyl-chain length was different from that of **3a** but having the same configuration as that of **3a** at C1′, showed synergistic activity as well as that of **3a** (Fig. 3). These results demonstrate that the synergistic activity of LL-P880γ depended on the absolute configuration at C1′ (*S*) of LL-P880γ.

Experimental

All melting points (mp) are uncorrected. NMR spectra were taken with a JEOL-JNM GSX 270 spectrometer and unless otherwise stated, tetramethylsilane was used as the internal standard. Mass spectra were obtained with a JMS-AX 500 mass spectrometer, and IR spectra were measured with a Perkin Elmer FT-IR 1760X spectrometer.

(−)-3-O-Benzyl-5-deoxy-5-C-methyl-1,2-O-isopropylidene-α-D-xylofuranose (**9**). A mixture of **8**[7] (9.67 g, 35 mmol) and Raney nickel (W-4 type, *ca.* 1.5 g) in MeOH (100 ml) was shaken in hydrogen for 2 h under 1 atm of pressure. After removing the catalyst by filtration, the filtrate was evaporated to give an oil, which was chromatographed on silica gel with hexane–EtOAc (9:1) to afford **9** (9.06 g, 93%) as colorless needles, mp 40°C, $[\alpha]_D^{28}$ −55° (*c* 2.55, EtOH). IR ν_{max} (KBr disk) cm^{-1}: 2972, 1498, 1374, 1256, 1215, 1167, 1132, 1076, 1020. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.0 Hz, CH_3), 1.32 and 1.48 (3H×2, s, $(CH_3)_2C$), 1.66–1.83 (2H, m, 5-CH_2), 3.79 (1H, d, J=3.1 Hz, 3-H), 4.06 (1H, dt, J=3.1, 7.0 Hz, 4-H), 4.48 and 4.71 (1H×2, d, J=11.9 Hz, CH_2 Ph), 4.61 (1H, d, J=3.7 Hz, 2-H), 5.91 (1H, d, J=3.7 Hz, 1-H), 7.33 (5H, m, Ar). *Anal.* Found: C, 69.16; H, 8.02%. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97%.

(−)-3-O-Benzyl-5-deoxy-5-C-propyl-1,2-O-isopropylidene-α-D-xylofuranose (**13**). Olefin **12** (*E*/*Z* 3:1) was prepared by the Wittig reaction of aldehyde **11** with *n*-propyltriphenylphosphonium bromide by the reported procedure in a 56% yield.[4] The hydrogenation of **12** was carried out by the same procedure as that described for the preparation of **9** to give **13** in a 95% yield as an oil, $[\alpha]_D^{26}$ −80° (*c* 1.77, benzene). IR ν_{max} (KBr disk) cm^{-1}: 2956, 1456, 1374, 1256, 1215, 1165, 1131, 1078, 1025. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, CH_3), 1.15–1.45 (4H, m, CH_2CH_2Me), 1.32 and 1.49 (3H×2, s, $(CH_3)_2C$), 1.74 (2H, m, 5-CH_2), 3.77 (1H, d, J=3.1 Hz, 3-H), 4.11 (1H, dt, J=3.1, 7.0 Hz, 4-H), 4.48 and 4.70 (1H×2, d, J=12.2 Hz, CH_2 Ph), 4.61 (1H, d, J=4.0 Hz, 2-H), 5.91 (1H, d, J=4.0 Hz, 1-H), 7.33 (5H, m, Ar). *Anal.* Found: C, 70.67; H, 8.59%. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55%.

(−)-(6S,1′S,2′R)-6-(1′,2′-Dihydroxybutyl)-4-methoxy-5,6-dihydropyran-2-one (**10**) *and (−)-(6S,1′S,2′R)-6-(1′,2′-dihydroxyhexyl)-4-methoxy-5,6-dihydropyran-2-one* (**14**). Each title compound was prepared by the reported method[4] from corresponding intermediates **9** and **13**, respectively. **10** was produced in a 9% overall yield from **9**, mp 141°C, $[\alpha]_D^{27}$ −72° (*c* 1.03, EtOH). IR ν_{max} (KBr disk) cm^{-1}: 3505, 3450, 3375, 2961, 1692, 1621, 1386, 1228. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.3 Hz, 4′-CH_3), 1.62 (2H, q, J=7.3 Hz, 3′-CH_2), 2.41–2.60 (2H, broad s, OH), 2.32 (1H, dd, J=17.1, 3.7 Hz, 5-H), 2.91 (1H, ddd, J=17.1, 12.7, 1.5 Hz, 5-H), 3.52

(1H, m, 1'-H), 3.53–3.77 (1H, m, 6-H), 3.77 (3H, s, OCH_3), 4.51 (1H, tt, J=4.0, 2.1 Hz, 2'-H), 5.14 (1H, d, J=1.5 Hz, 3-H). *Anal.* Found: C, 55.72; H, 7.60%. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46%. **14** was produced in a 15% overall yield from **13**, mp 132°C, $[\alpha]_D^{26}$ −61° (*c* 0.67, EtOH). IR ν_{max} (KBr disk) cm^{-1}: 3558, 3403, 2934, 1680, 1620, 1397, 1228. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, t, J=7.0 Hz, 6'-CH_3), 1.35 (2H, m, 5'-CH_2), 1.62–1.64 (4H, m, 3'- and 4'-CH_2), 2.32 (1H, dd, J=17.1, 3.7 Hz, 5-H), 2.40–2.55 (2H, broad s, OH), 2.90 (1H, ddd, J=17.1, 12.8, 1.8 Hz, 5-H), 3.50 (1H, dd, J=4.0, 2.4 Hz, 1'-H), 3.77 (3H, s, OCH_3), 3.77–3.80 (1H, m, 6-H), 4.53 (1H, tt, J=4.0, 2.1 Hz, 2'-H), 5.14 (1H, d, J=1.8 Hz, 3-H). *Anal.* Found: C, 59.18; H, 8.38%. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.

Synthesis of LL-P880γ (**3**) *and its analogues* (**4a** *and* **5a**)

These title compounds were prepared by the reported methods[5] from corresponding LL-P880β (**2**) and its analogues (**10** and **14**).

(−)-(*1'S,2'R*)-*LL-P880γ* (**3a**)[1,2] was produced in a 27% overall yield from **2a**,[4] mp 114–115 C (lit.[2] 116–118°C). $[\alpha]_D^{27}$ −32° (*c* 0.63, MeOH) (lit.[2] −31°, MeOH). IR (KBr disk) cm^{-1}: 3398, 2961, 1712, 1651, 1569, 1250, 1132. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=6.7 Hz, -CH_3), 1.37–1.68 (4H, m, 3'- and 4'-CH_2), 2.82 (1H, broad s, OH), 3.34 (1H, broad s, OH), 3.81 (3H, s, OCH_3), 4.02 (1H, m, 2'-H), 4.23 (1H, d, J=2.1 Hz, 1'-H), 5.42 (1H, d, J=2.1 Hz, m, 5-H), 6.21 (1H, d, J=1.2 Hz, 3-H).

(+)-(*1'R,2'R*)-*LL-P880γ* (**3b**) was produced in a 29% yield from **2b**,[5] mp 65–66 C, $[\alpha]_D^{26}$ +79° (*c* 0.32, EtOH). The spectral data (IR and ^{1}H-NMR) were identical with the reported data.[4]

(+)-(*1'R,2'S*)-*LL-P880γ* (**3c**) was produced in a 27% yield from **2c**,[6,8] mp 114–115 C, $[\alpha]_D^{27}$ +33° (*c* 0.56, MeOH). The spectral data (IR, ^{1}H-NMR and MS) were similar to those of **3a**. *Anal.* Found: C, 58.02; H, 7.13%. Calcd. for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07%.

(−)-(*1'S,2'R*)-*4-Methoxy-6-(1',2'-dihydroxybutyl)pyran-2-one* (**4a**) was produced in a 19% overall yield from **10**, mp 138–139°C, $[\alpha]_D^{25}$ −51° (*c* 0.50, EtOH). IR ν_{max} (KBr disk) cm^{-1}: 3385, 3292, 1730, 1704, 1644, 1562, 1452, 1407, 1240, 1144. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.3 Hz, 4'-CH_3), 1.64 (2H, q, J=7.3 Hz, 3'-CH_2), 2.75–3.00 (2H, broad s, OH), 3.82 (3H, s, OCH_3), 3.92–3.98 (1H, m, 2'-H), 4.27 (1H, d, J=2.5 Hz, 1'-H), 5.43 (1H, d, J=2.4 Hz, 5-H), 6.19 (1H, d, J=1.2 Hz, 3-H). EIMS *m/z*: 215 (M^++1), 185, 155, 125. *Anal.* Found: C, 56.19; H, 6.69%. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59%.

(−)-(*1'S,2'R*)-*6-(1',2'-Dihydroxyhexyl)-4-methoxypyran-2-one* (**5a**) was produced in a 25% overall yield from **14**, mp 104–105°C, $[\alpha]_D^{26}$ −13° (*c* 0.61, EtOH). IR ν_{max} (KBr disk) cm^{-1}: 3368, 1743, 1714, 1652, 1572, 1456, 1409, 1250, 1120. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.0 Hz, 6'-CH_3), 1.32–1.48 (2H, m, 5'-CH_2-), 1.59–1.79 (4H, m, 3'- and 4'-CH_2-), 2.72–3.95 (1H, broad s, OH), 3.82 (3H, s, OCH_3), 4.00–4.04 (1H, m, 2'-H), 4.24 (1H, d, J=2.1 Hz, 1'H), 5.43 (1H, d, J=2.1 Hz, 5-H), 6.19 (1H, d, J=1.2 Hz, 3-H). EIMS *m/z*: 243 (M^++1), 225, 155, 125. *Anal.* Found: C, 59.63; H, 7.63%. Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49%.

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