

## HIGHLY STEREOSELECTIVE SYNTHESIS AND STRUCTURAL CONFIRMATION OF A FUNGAL METABOLITE, LL-P880 $\beta$

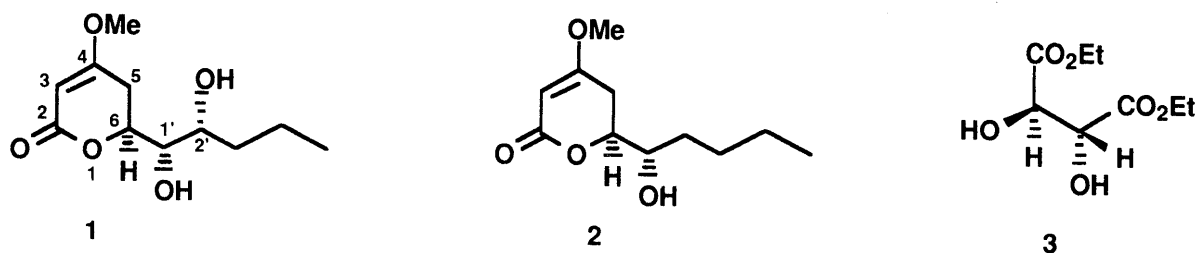
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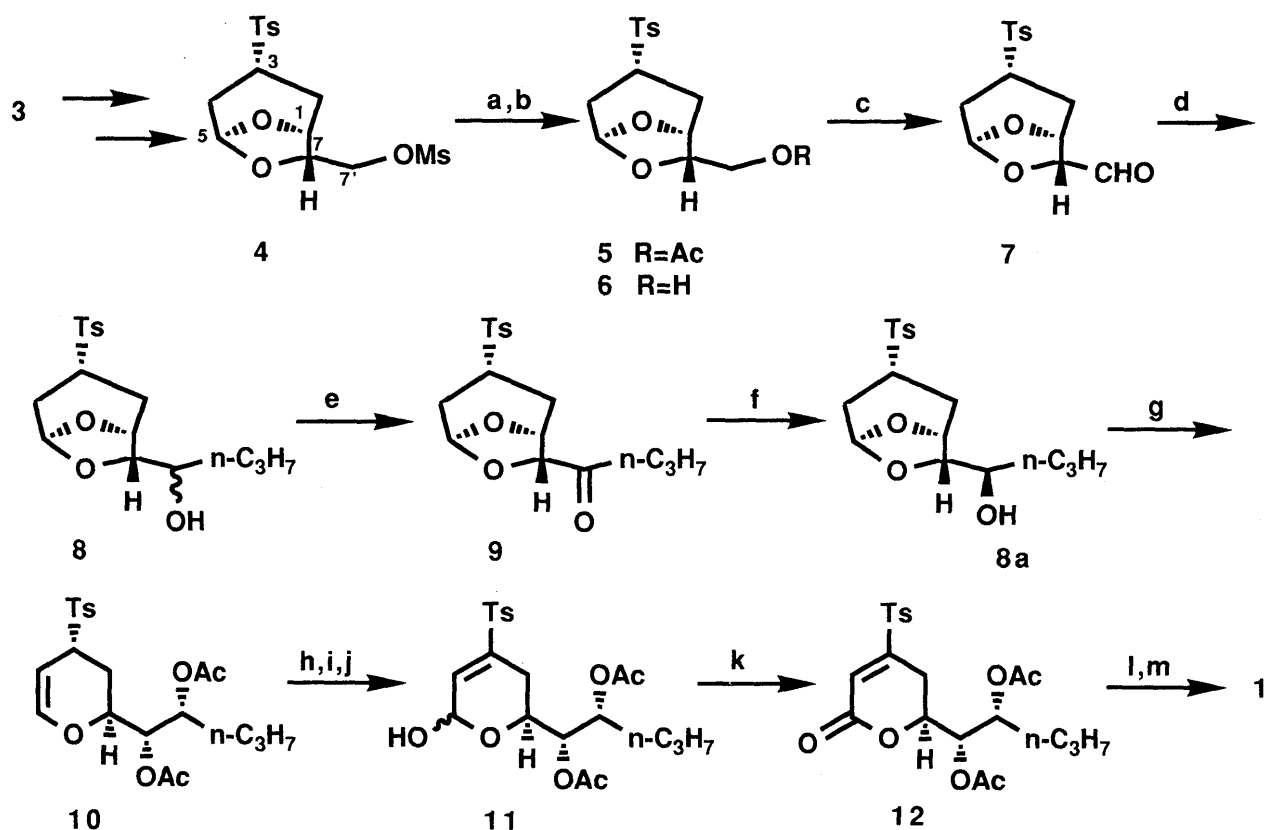
A fungal metabolite, LL-P880 $\beta$  [6*S*-(1'*S*,2'*R*-dihydroxypentyl)-4-methoxy-5,6-dihydropyran-2-one] (**1**), was synthesized unambiguously from diethyl (*R,R*)-tartrate (**3**) as a chiral pool *via* highly stereoselective construction of the C7'-asymmetric carbon of the intermediate 6,8-dioxabicyclo[3.2.1]octane derivative (**8a**), and the stereochemistry of the C6-chiral center of the metabolite was chemically confirmed as (*S*).

**KEYWORDS** fungal metabolite; LL-P880 $\beta$ ; chiral synthesis; diethyl (*R,R*)-tartrate; structural confirmation

A group of 6-substituted 5,6-dihydro-2-pyrones have widely occurred in plants and fungi and possess a diverse range of biological activity.<sup>1)</sup> Especially those with oxygen functions on the pyrone ring and C6-side chain are known to exhibit plant growth inhibitory, antifungal, and antitumor activities. Among them, LL-P880 $\beta$  (**1**) is one of the minor metabolites of an unidentified *Penicillium* species,<sup>2)</sup> which also produces its mono-hydroxylated analogue pestalotin (**2**) [LL-P880 $\alpha$ ], a potent gibberellin synergist, as the major metabolite.<sup>3)</sup> The absolute structure of the compound (**1**) has been proposed to be 6*S*, 1'*S*, and 2'*R* as indicated on the basis of spectral data of the CD and NMR as well as of those data for its di-dehydroxylated olefin.<sup>2)</sup> None of the precedent syntheses of **1**, however, starting from the appropriate chiral pools, (*R,R*)-tartaric acid,<sup>4a)</sup> D-glucose,<sup>4b)</sup> and D-idose,<sup>4c)</sup> chemically established the absolute configuration of the C6-carbon, due to non-stereoselective asymmetric construction of the chiral center. We wish to disclose here a highly stereoselective total synthesis of LL-P880 $\beta$  (**1**) using diethyl (*R,R*)-tartrate (**3**) as the chiron with the C6- and C1'-asymmetric carbons for **1**.



Chiral 7-mesyloxymethyl-3-tosyl-6,8-dioxabicyclo[3.2.1]octane (**4**) was prepared in 54% overall yield from diethyl (*R,R*)-tartrate (**3**) *via* a 4-step sequence of reactions according to the reported method.<sup>5a)</sup> The C7'-carbon functionality was transformed to the aldehyde (**7**) *via* 7'-O-acetate (**5**) and 7' - alcohol (**6**) by the usual methods including acetoxylation, hydrolysis, and Swern oxidation in



(a) AcOK / 18-crown-6 / DMF / 80 °C / 12 h (95%); (b) K<sub>2</sub>CO<sub>3</sub> / MeOH / r.t. / 12 h (86%); (c) (COCl)<sub>2</sub> / DMSO / Et<sub>3</sub>N / -78→0 °C / 5 h (85%); (d) *n*-C<sub>3</sub>H<sub>7</sub>MgBr / THF / 0 °C / 1 h (88%); (e) Jones reagent / 0 °C / 1 h (87%); (f) L-Selectride / THF / -78 °C / 2 h (quant.); (g) BF<sub>3</sub>-Et<sub>2</sub>O / Ac<sub>2</sub>O / CH<sub>2</sub>Cl<sub>2</sub> / 0 °C / 1 h (81%); (h) Br<sub>2</sub> / CH<sub>2</sub>Cl<sub>2</sub> / 0 °C / 5 min; (i) K<sub>2</sub>CO<sub>3</sub> / THF-H<sub>2</sub>O / 0 °C / 15 min; (j) NaOMe / THF / 0 °C / 40 min (overall 58% in 3 steps: h, i, j); (k) Jones reagent / 0 °C / 1 h (83%); (l) K<sub>2</sub>CO<sub>3</sub> / MeOH / 0 °C / 5 min; (m) NH<sub>3</sub> / MeOH / r.t. / 2 d (overall 38% in 2 steps: l, m)

69% overall yield. Alkylation of the aldehyde (**7**) with *n*-PrMgBr in THF at 0 °C gave a diastereomeric mixture of the carbinols (**8**) with poor stereoselectivity (*erythro:threo*=*ca.*4:3 (for structural determination of the epimers, *vide infra*)). Stereoselective formation of the *threo*-isomer (**8a**), which is the desired intermediate for synthesis of **1**, was realized by reduction of the 7'-ketone (**9**). Thus, the 7'-ketone (**9**) prepared by Jones oxidation of the epimeric carbinols (**8**) was reduced stereoselectively with L-selectride [LiB(sec-Bu)<sub>3</sub>H] in THF at -78 °C to afford crystalline alcohols (**8**) (*erythro* : *threo* = 1 : 25). Purification by recrystallization gave the *threo*-alcohol (**8a**) [mp 128 °C, [α]<sub>D</sub> -46.0° (CHCl<sub>3</sub>)], the structure of which was established by X-ray crystallography.<sup>6)</sup>

Analogously with the synthesis of (+)-pestalotin (**2**),<sup>5b)</sup> transformation of the bicyclic (**8a**) to the pyranoid (**10**) was achieved by acetolysis in the presence of BF<sub>3</sub>-Et<sub>2</sub>O in good yield. Successive treatment of **10** with Br<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> in aqueous THF, and NaOMe in THF, converted the pyranil moiety of **10** into the epimeric mixture of hemiacetals (**11**) in 58% overall yield. The 4-sulfonyl-2-pyrone derivative (**12**), obtained by Jones oxidation of **11**, was treated carefully with K<sub>2</sub>CO<sub>3</sub> in MeOH

for a short period of 5 min at 0 °C to produce a crude mixture of products<sup>7)</sup> which was successively treated with ammonia-saturated MeOH at room temperature to give 38% overall yield of (-)-LL-P880 $\beta$  (**1**) [mp 134-135 °C;  $[\alpha]_D$  -59.6 ° (MeOH), lit. <sup>2a)</sup> mp 135.5-136 °C;  $[\alpha]_D$  -59.8 ° (MeOH)] which was identified with the natural product in all respects.<sup>2b)</sup> The present synthesis stands for not only the first stereoselective synthesis of **1** but also the first chemical confirmation of the absolute configuration of C6 as (6*S*).

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## REFERENCES AND NOTES

- 1) M.T. Davies-Coleman, D.E.A. Rivett, "Progress in the Chemistry of Organic Natural Products," W. Herz, H. Grisebach, G.W. Kirby, Ch. Tamm, ed., Vol. 55, pp. 1-35, Springer-Verlag (1989).
- 2) a) W.J. McGahren, G.A. Ellestad, G.O. Morton, M.P. Kunstmann, P. Mullen, *J. Org. Chem.*, **38**, 3542 (1973); b) Y. Kimura, T. Hamasaki, H. Nakajima, *Agric. Biol. Chem.*, **50**, 1649 (1986).
- 3) G.A. Ellestad, W.J. McGahren, M.P. Kunstmann, *J. Org. Chem.*, **37**, 2045 (1972); Y. Kimura, S. Tamura, *Agric. Biol. Chem.*, **36**, 1925 (1972).
- 4) a) H. Meyer, D. Seebach, *Liebigs Ann. Chem.*, **1975**, 2261; b) M. Kirihata, K. Ohta, I. Ichimoto, H. Ueda, *Agric. Biol. Chem.*, **54**, 2401 (1990); c) M. Kirihata, Y. Kamihisa, I. Ichimoto, H. Ueda, *Chemistry Express*, **7**, 837 (1992).
- 5) a) Y. Masaki, K. Nagata, K. Kaji, *Chem. Lett.*, **1983**, 1835; Y. Masaki, I. Iwata, T. Imaeda, H. Oda, H. Nagashima, *Chem. Pharm. Bull.*, **36**, 1241 (1988); b) Y. Masaki, K. Nagata, Y. Serizawa, K. Kaji, *Tetrahedron Lett.*, **25**, 95 (1984).
- 6) Crystal data for (-)-**8a**: C<sub>17</sub>H<sub>24</sub>O<sub>5</sub>S, M=340.43, colorless prism, space group P2<sub>1</sub>2<sub>1</sub>2(#18) with a=8.08(1), b=34.56(1), c=6.15(1), V=1716(3) Å<sup>3</sup>, Z=4, D<sub>c</sub>=1.317/cm<sup>3</sup>, R=0.051 for 1202 reflections.
- 7) Although the crude products obtained by the careful basic treatment contained not only the desired LL-P880 $\beta$  (**1**) but also the diacetate of **1**, prolonged treatment of **12** with K<sub>2</sub>CO<sub>3</sub> in MeOH resulted in the formation of intractable materials.

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