HIGHLY STEREOSELECTIVE SYNTHESIS AND STRUCTURAL CONFIRMATION OF A FUNGAL METABOLITE, LL-P880β

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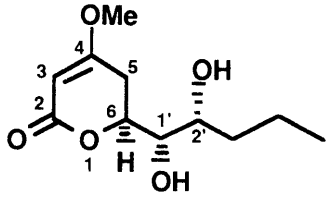
A fungal metabolite, LL-P880β [6S-(1'*S*,2'*R*-dihydroxypentyl)-4-methoxy-5,6-dihydropyran-2-one] (**1**), was synthesized unambiguously from diethyl (*R*,*R*)-tartrate (**3**) as a chiral pool *via* highly stereoselective construction of the C7'-asymmetric carbon of the intermediate 6,8-dioxabicyclo[3.2.1]octane derivative (**8a**), and the stereochemistry of the C6-chiral center of the metabolite was chemically confirmed as (*S*).

KEYWORDS fungal metabolite; LL-P880β; 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.[1] 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-P880β (**1**) is one of the minor metabolites of an unidentified Penicillium species,[2] which also produces its mono-hydroxylated analogue pestalotin (**2**) [LL-P880α], a potent gibberellin synergist, as the major metabolite.[3] 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.[2] None of the precedent syntheses of **1**, however, starting from the apropriate chiral pools, (*R*,*R*)-tartaric acid,[4a] D-glucose,[4b] and D-idose,[4c] 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-P880β (**1**) using diethyl (*R*,*R*)-tartrate (**3**) as the chiron with the C6- and C1'-asymmetric carbons for **1**.



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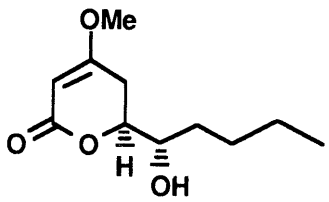

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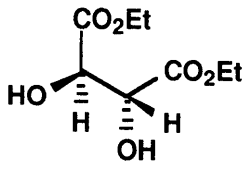

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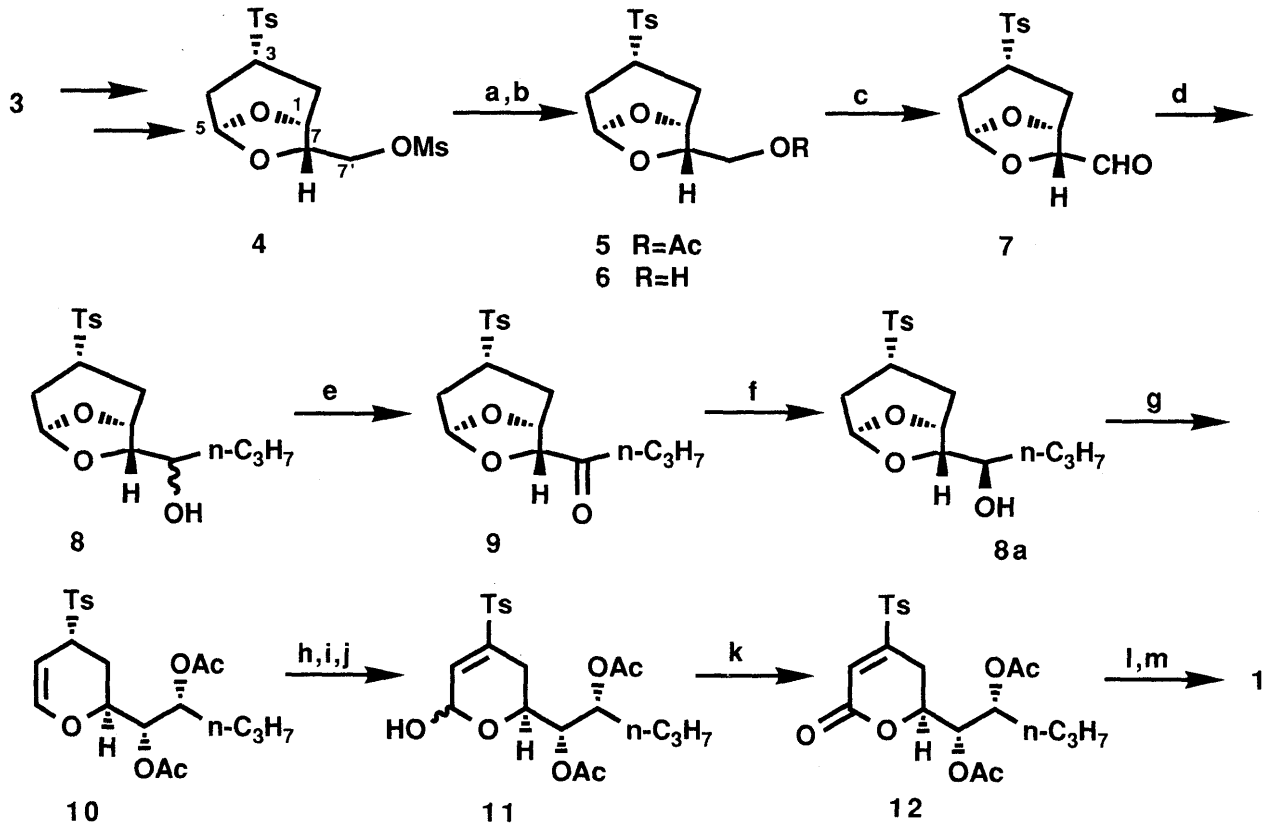
Chiral 7-mesyloxymethyl-3-tosyl-6,8-dioxabicyclo[3.2.1]octane (**4**) was prepared in 54% overall yield from diethyl (*R*,*R*)-tartrate (**3**) *via* a 4-step sequence of reactions according to the reported method.[5a] The C7'-carbon functionality was transformed to the aldehyde (**7**) *via* 7'-O-acetate (**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_2CO_3 / MeOH / r.t. / 12 h (86%) ; (c) $(COCl)_2$ / DMSO / Et_3N / -78→0 °C / 5 h (85%) ; (d) *n*-C_3H_7MgBr / 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_3-Et_2O /Ac_2O /CH_2Cl_2 / 0 °C / 1 h (81%) ; (h) Br_2 / CH_2Cl_2 / 0 °C / 5 min ; (i) K_2CO_3 / THF-H_2O / 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_2CO_3 / MeOH / 0 °C / 5 min ; (m) NH_3 / 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)3H] 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, $[\alpha]_D$ -46.0 ° ($CHCl_3$)], the structure of which was established by X-ray crystallography.[6)]

Analogously with the synthesis of (+)-pestalotin (**2**),[5b)] transformation of the bicyclic (**8a**) to the pyranoid (**10**) was achieved by acetolysis in the presence of BF3-Et2O in good yield. Successive treatment of **10** with Br2 and K2CO3 in aqueous THF, and NaOMe in THF, converted the pyranyl 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 K2CO3 in MeOH

for a short period of 5 min at 0 °C to produce a crude mixture of products[7] which was successively treated with ammonia-saturated MeOH at room temperature to give 38% overall yield of (-)-LL-P880β (**1**) [mp 134-135 °C; $[\alpha]_D$ -59.6 ° (MeOH), lit. [2a] mp 135.5-136 °C; $[\alpha]_D$ -59.8 ° (MeOH)] which was identified with the natural product in all respects.[2b] 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*).

ACKNOWLEDGEMENTS The X-ray crystallography for the single crystal of **8a** was performed by Dr. M. Shiro, Rigakudenki Co. Ltd., to whom the authors are deeply indebted. A sample of natural (-)-LL-P880β (**1**) was provided by Professor Y. Kimura, Dept. of Agricultural Chemistry, Tottori University, whose help the authors greatly appreciate. This work was supported in part by a Grant-in-Aid for Scientific Research to Y.M. (No. 02670958) from the Ministry of Education, Science and Culture of Japan.

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6) Crystal data for (-)-**8a**: $C_{17}H_{24}O_5S$, M=340.43, colorless prism, space group $P2_12_12$(#18) with a=8.08(1), b=34.56(1), c=6.15(1), V=1716(3) Å, Z=4, D_c=1.317/cm^3, R=0.051 for 1202 reflections.

7) Although the crude products obtained by the careful basic treatment contained not only the desired LL-P880β (**1**) but also the diacetate of **1**, prolonged treatment of **12** with K_2CO_3 in MeOH resulted in the formation of intractable materials.

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