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Synthesis and Absolute Configuration of Phomozin

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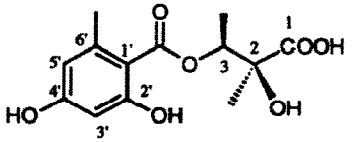
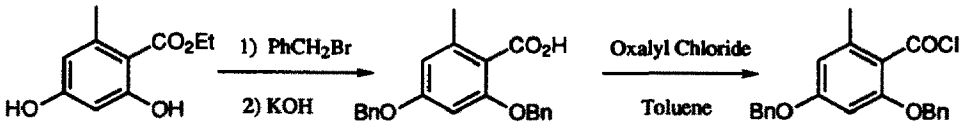
Abstract: The absolute configuration of the fungal phytotoxin phomozin has been unambiguously determined by the synthesis of its two enantiomers.

Phomopsis helianthi is a fungus that causes necrosis and stem cankering of sunflower. *Phomozin* **1** was recently isolated from culture filtrates of this severe pathogen.[1,2] The structure of **1** was determined from X-ray diffraction[3] and other physical data, and by comparison with dimethyl glyceric acid and was identified as *erythro* .[4] However, according to the authors, the poor quality of crystals obtained did not allow them to assign the absolute configuration with total confidence. We thus considered interesting to synthesize the enantiomers of *erythro* 3-(2',4'-dihydroxy-6'-methylbenzoyloxy)-2-hydroxy-2-methylbutanoic acid. We now wish to report the absolute configuration of **1** along with a facile synthesis of chiral *phomozin*.



1

The aromatic fragment **4**[5] was obtained from commercially available ethyl orcelinate **2** by benzylation[6] ($PhCH_2Br$, K_2CO_3, acetone, reflux, 12h, 99%), alkaline hydrolysis (KOH, $EtOH/H_2O$, RT, 24h, 85%) and treatment with oxalyl chloride (cat. DMF, RT, toluene, 10 min).



2 **3** **4**

Homochiral **5a** (2S,3S) and **5b** (2R,3R) were synthesized from lactic acid using the previously reported dioxolanone methodology.[7]

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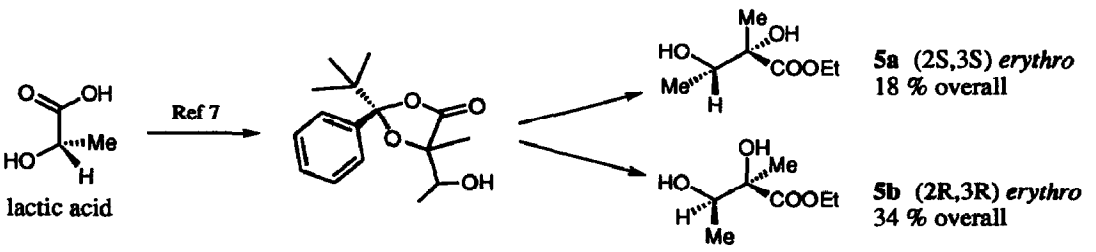
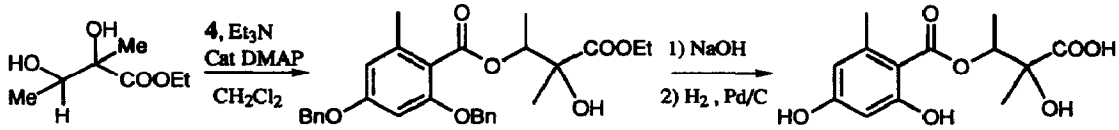


Coupling of the hindered diols **5a** or **5b** with **4** (Et_3N, cat. DMAP, CH_2Cl_2, 0°C, 10 min) has to be run under strictly anhydrous conditions to minimize the formation of the remarkably stable anhydride of **3**. Selective saponification (NaOH, EtOH, Et_2O, 12h) and hydrogenolysis (H_2, Pd/C, EtOAc, 9 bars, 5h) allows the isolation of the desired targets.[5,8]



5a (2S,3S)	**6a** (2S,3S)	30%	**7a** (2S,3S) 48% (2 steps)
5b (2R,3R)	**6b** (2R,3R)	20%	**7b** (2R,3R) 42% (2 steps)

Compounds **1**, **7a** and **7b** have the following specific rotations[9] :

1 $[\alpha]^{20}_D = +28$ (D_2O, c=0.316)[1]
7a $[\alpha]^{20}_D = +25{,}5$ (D_2O, c=0.325)
7b $[\alpha]^{20}_D = -27$ (D_2O, c=0.325)

These data allow with total confidence the conclusion that *Phomozin* is (2S,3S) 3-(2',4'-dihydroxy-6'-methylbenzoyloxy)-2-hydroxy-2-methylbutanoic acid.

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References and notes

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2 Mazars, C.; Canivenc, E.; Rossignol, M.; Auriol, P. *Plant Science* **1991**, *75*, 155-160.
3 Declercq, J.P.; Klaebe, A.; Rossignol, M.; Mazars, C. *Acta Crystallogr., Sect C:* **1991**, *C47*, 470-472.
4 **1** is identified as "*erythro* (11S,10R)" in Ref. 1 (corresponding to the X-ray diffraction atom labelling) but the PLUTO drawing represents the (11S,10S) enantiomer.
5 All compounds gave satisfactory analyses.
6 Hendrickson, J.B.; Ramsay, M.V.J.; Kelly, T.R. *J. Am. Chem. Soc.* **1972**, *94*, 6834-6843.
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8 Spectral data were compatible with previously published data[1]. **7a**: mp 89-92°C; ^1H NMR (250 MHz, D_2O): δ 6.20 (1H, s), 6.16 (1H, s), 5.38 (1H, q, J=6.5Hz), 2.34 (3H, s), 1.40 (3H, s), 1.32 (3H, d, J=6.5Hz); ^{13}C NMR (62.5 MHz, D_2O): δ 182.5, 173.5, 164.4, 163.0, 146.4, 114.0, 109.2, 103.2, 80.2, 79.0, 25.6, 25.2, 17.3.
9 Optical rotations were taken in D_2O in order to be consistent with the conditions of the original value.[1]

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