Pergamon

Tetrahedron Letters, Vol. 35, No. 44, pp. 8171-8172, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01802-2

Diastereoselective Synthesis of a Methylated Derivative of Phomozin, a Phytotoxin Isolated from *Phomopsis helianthi*, a Phytopathogenic Fungus of Sunflowers

Robert Nouguier*, Michèle P. Bertrand*, Philippe Picon and Patricia Perfetti

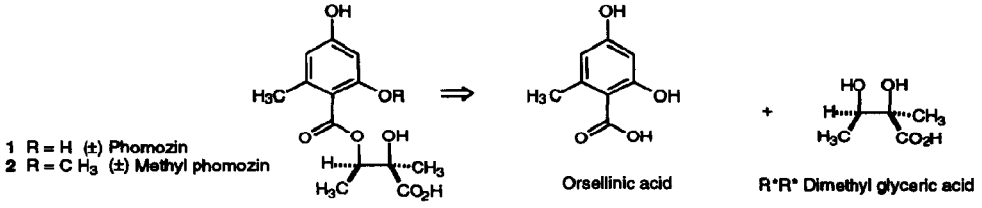
Laboratoire de Chimie Moléculaire Organique, Faculté Saint Jérôme, Avenue Normandie-Niemen

13397 Marseille Cedex 20, France

Keywords : Phomozin, orsellinic acid, dimethylglyceric acid, Phomopsis helianthi.

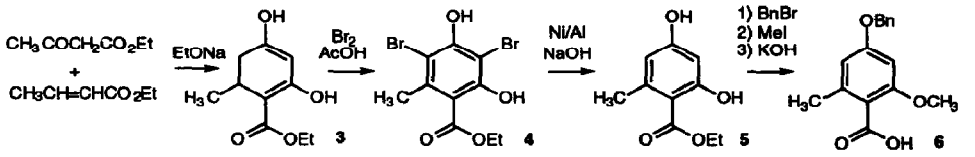
Abstract : A methylated derivative of the phytotoxin phomozin (**2**) is synthesized in high yield *via* the regioselective coupling of 2-methyl-4-benzyl orsellinic acid (**6**) and (*R**, *R**) benzyl dimethylglycerate (**9**) and one step hydrogenolysis of the benzyl and benzoyl protection.

(+)-Phomozin (**1**) has been isolated from culture filtrates of *Phomopsis helianthi* and identified by ^{1}H, ^{13}C NMR, mass spectrometry and X-ray diffraction.[1] The absolute configuration of the two asymmetric carbons could not be determined by X-ray, but very recently[2] the *erythro* configuration (2*S*, 3*S*) was unambiguously assigned to the dimethylglyceric acid moiety.



The difficulty to isolate and purify multigram quantities of the natural toxin from culture filtrates, the need of large amounts to test the resistance of new varieties of sunflowers plants to the toxin, and the unstability of the natural product which decomposes on standing at room temperature, led us to investigate the synthesis of the more stable methyl phomozin ((±)-**2**). The goal was to check the phytotoxicity of (±)-**2** compared to that of (±)-**1** or (+)-**1** in the resistance tests of sunflower plants.

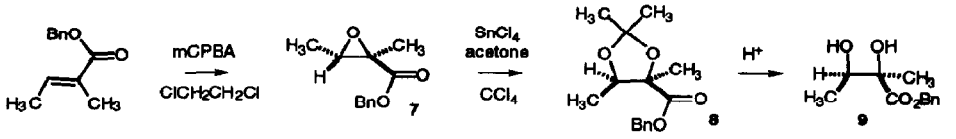
The orsellinic moiety has been prepared by various methods[3] and the ethyl ester is now commercially available. These routes are not suitable for large scale developments; therefore we used a three step method for the synthesis of **5** :[4]



The condensation of ethyl crotonate and ethyl acetoacetate (EtONa, EtOH at 80°C) yielded **3** which was brominated and reduced into **5**. Subsequent one-pot selective monobenzylation (BnBr, K_2CO_3, acetone, RT,

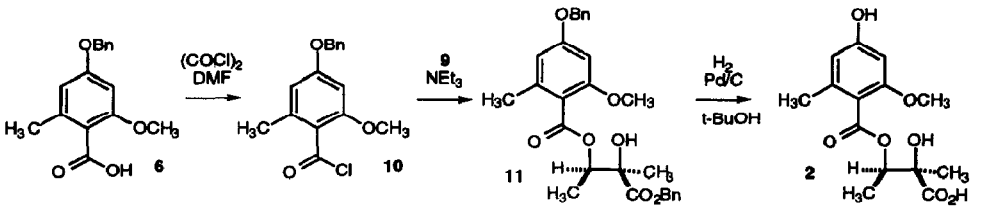
12h) followed by methylation (CH_3I, 5 equiv in portions, 40°C 12h), and saponification with KOH in glycol (8h at reflux), led to the desired protected acid **6** (70% yield for the three last steps after purification of **6**).

The synthesis of **9** was achieved in 3 steps using the common tiglic acid as starting material with 65% yield for the 3 steps. The reaction of the epoxide **7** with $SnCl_4$ in acetone[5] is entirely diastereoselective.



The coupling of **6** with (*R*,R**)-**9** proved to be very efficient and regioselective provided that one equivalent of the acid chloride **10** (prepared from **6** with 1.2 equiv of $(COCl)_2$ in the presence of catalytic amounts of DMF in CH_2Cl_2, -40°C to RT, 6h) was slowly added to a solution of one equivalent of **9** in CH_2Cl_2 and 3 equiv of NEt_3 (-40°C to RT 12h). **11** was then obtained in 87% yield after purification.

Total hydrogenolysis of **11** (H_2, 1atm), readily effected in 5h at 40°C, on Pd/C in *t*-BuOH, in the presence of a few drops of AcOH, yielded the desired methyl phomozin **2** in quantitative yield after purification (silicagel, $CHCl_3$-AcOH, 7/3).



The synthesis of the orsellinic acid derivative **6** and of benzyl dimethylglycerate **9** were carried out on a 1 mole scale and the coupling reaction was effected on a 3 g scale of final product. This pathway constitutes a very effective, selective and high yielding method for the synthesis of methyl phomozin **2**.

The phytotoxicity of (±)-**2** is currently tested and compared to the phytotoxicity of the natural product. If ever the resistance tests were unsatisfactory, we have now in hand a valuable[6] methodology for synthesizing (±)-phomozin (*via* dibenzylation of **5**). The same strategy would allow, *if necessary*, to prepare the (*S*, *S*) enantiomer of methyl phomozin or phomozin, from (2*S*, 3*S*) benzyl dimethyl glycerate obtained from the optically pure epoxide **7** (2*S*, 3*R*).[7]

Acknowledgments. Financial assistance from Sanofi Elf Bio-Recherches is gratefully acknowledged.

References and notes :

1. Mazars, C.; Rossignol, M.; Auriol, P.; Klaebe, A. *Phytochemistry*, **1990**, *29*, 3441-44. Mazars, C.; Canivenc, E.; Rossignol, M.; Auriol, P. *Plant Science*, **1991**, *75*, 155-60. Declercq, J. P.; Klaebe, A.; Rossignol, M.; Mazars, C. *Acta Cryst.* **1991**, *C47*, 470-72.
2. Vicart, N.; Ortholand, J.-Y.; Emeric, G.; Greiner, A. *Tetrahedron Lett.* **1994**, *35*, 3917-18.
3. Tyman, J. H. P.; Durrani, A. A. *Tetrahedron Lett.* **1973**, *49*, 4839-40. Kloss, R. A.; Clayton, D. A. *J. Org. Chem.* **1965**, *30*, 3566-67. Solladié, G.; Rubio, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron : Asym.* **1990**, *1*, 187-198.
4. Santesson, J. *Acta Chem. Scand.* **1970**, *24*, 3373-78. Gaucher, G. M.; Shepherd, M. G. *Biochem. Prep.* **1971**, *13*, 70-74.
5. Ishizuka, N. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 813-26.
6. In the recently reported synthesis of (+)-phomozin (ref 2), the yields of the coupling reaction and of the two step deprotection are not high (respectively 30 and 48%)
7. The asymmetric epoxidation of acrylic type esters of suitably protected carbohydrates is currently investigated in our laboratory.

(*Received in France* 8 *September* 1994; *accepted* 9 *September* 1994)