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## TOTAL SYNTHESIS OF THE CYCLODEPSIPEPTIDE IONOPHORE PITHOMYCOLIDE<sup>1</sup> Magdi M. Moussa and Philip W. Le Quesne\* Department of Chemistry and Barnett Institute, Northeastern University Boston, MA 02115-5096, U.S.A.

Abstract: The total synthesis of pithomycolide 1, a structurally unique ionophoric depsipeptide from the fungus <u>Pithomyces chartarum</u>, is described. Copyright © 1996 Elsevier Science Ltd

Pithomycolide <u>1</u> is a cyclodepsipeptide metabolite of the pasture fungus <u>Pithomyces chartarum</u> (Berk. and Curt.) M.B. Ellis, where it accompanies the hepatotoxic sporidesmins, represented by <u>2</u> and <u>3</u>. Chemical degradation of pithomycolide established structure <u>1</u>,<sup>2</sup> which, apart from the subsequently



discovered congeneric value analogue  $4,^3$ , remains a unique depsipeptide type in the literature. Our interest in the synthesis of <u>1</u> was kindled by finding that it binds Na<sup>+</sup> and Ca<sup>2+</sup> strongly in organic solvents and K<sup>+</sup> less so.<sup>4</sup> Although x-ray structural investigations have been unfruitful, MMX calculations support a single, clearly defined lowest energy conformation for pithomycolide that is consonant with <sup>1</sup>H NMR and IR data.<sup>5</sup> We now report a total synthesis of <u>1</u> that enables the preparation of the parent compound and analogues suitable for biological evaluation.

The original degradative work<sup>2</sup> established that the ester bond incorporating the alanine residue in <u>1</u> is the most labile to acid and base-catalyzed hydrolysis. Accordingly we sought to prepare pithomycolide by macrolactonization of hydroxyacid 5.



Our main concerns were formation of both benzylic esters without racemization, the best order in which to assemble the five component residues in 5, and the macrolactonization itself. Experiment showed that 5 was best constructed by combining the two linked aromatic acids with fragment <u>6</u>. (cf. ref. 5).

S-(-)-3-Hydroxy-3-phenylpropanoic acid<sup>6</sup> was prepared from cinnamic acid <u>via</u> ( $\pm$ )-3-bromo-3phenyl-propanoic acid, which underwent acid hydrolysis and resolution <u>via</u> chymotrypsin-catalyzed hydrolysis of the derived ethyl esters (40% yield).<sup>7-10</sup> The allyl ester and TBDMS ether of this hydroxy-acid were condensed (DCC/DMAP) to give diester <u>7</u> (75% yield). That this condensation proceeded without racemization was shown by deprotection (HF/MeCN,<sup>11</sup> TPPTS/Pd(OAc)<sub>2</sub><sup>12, 13</sup>) and hydrolysis (0.1M KOH) to give S-(-)-3-hydroxy-3-phenylpropanoic acid of undiminished optical rotation. Deallylation of <u>7</u><sup>12,13</sup> gave acid <u>8</u> (58% yield).



Condensation of L-alanine allyl ester<sup>14</sup> with N-t-BOC-N-methyl-L-alanine (HOBT-Nmethylmorpholine)<sup>15</sup> gave, after selective removal of the BOC-group (HCl gas, EtOAc)<sup>16</sup> aminoester <u>9</u> in 55% yield. This was condensed, albeit with some difficulty, with the acetyl ester of L- $\alpha$ -hydroxyisovaleric acid (BOP-Cl, DIEA, CH<sub>2</sub>Cl<sub>2</sub>)<sup>17, 18</sup> the product then being selectively hydrolyzed (K<sub>2</sub>CO<sub>3</sub>, MeOH, H<sub>2</sub>O) to give <u>10</u> in 25% overall yield from <u>9</u>.



Diamide alcohol <u>10</u> reacted with silylated acid <u>8</u> (DCC/DMAP) to give the diprotected, linear hydroxyacid <u>11</u> (18% yield after extensive chromatography). Efficient deprotection (HF/MeCN<sup>11</sup>, TPPTS/Pd(OAc)<sub>2</sub><sup>12,13</sup>) gave <u>5</u>, which slowly underwent macrolactonization (BOP-Cl/CH<sub>2</sub>Cl<sub>2</sub>/DIEA)<sup>17,19</sup> to yield pithomycolide (11% yield after 48 h) identical with the natural product by chromatographic comparison, NMR, and mass spectrometry. No diastereomer at the new benzylic ester center was observed. The yield of pithomycolide can be increased by recycling starting material. Electrospray MS-MS of the synthetic compound confirmed the ionophoric properties observed<sup>4</sup> for the natural product. Further synthetic studies of the pithomycolide analog <u>4</u> and some non-natural relatives are now underway.

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## References and Notes

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