



Determination of the Absolute Stereochemistry of the Antifungal Antibiotic YM-47522 by the Total Synthesis of Its Enantiomer

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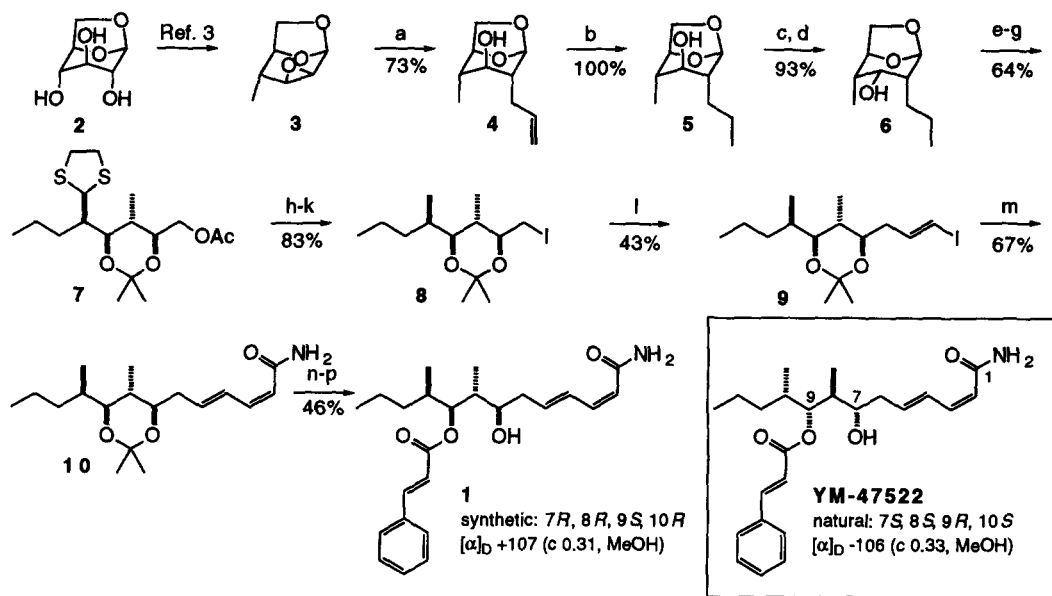
Abstract: The enantiomer **1** of the new antifungal antibiotic YM-47522 has been synthesized and found to be the antipode of the natural product. Thus, the absolute stereochemistry of the naturally occurring antibiotic YM-47522 was determined to be (7*S*, 8*S*, 9*R*, 10*S*).

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Recently, a group of Yamanouchi Pharmaceutical Co. has published the isolation of a novel, potent antifungal antibiotic YM-47522.¹ Extensive spectroscopic studies led the authors to establish the structure and the relative stereochemistry of the antibiotic,² while the absolute stereochemistry remained to be determined. We report herein the stereospecific synthesis of the arbitrarily chosen (7*R*, 8*R*, 9*S*, 10*R*) isomer **1** and hence the absolute stereochemistry of the natural antibiotic YM-47522.

Oxirane ring opening of the epoxide **3**,³ readily available from levoglucosan **2**, with diallylmagnesium⁴ proceeded mainly at C₂ to give the *gluco*-alcohol **4** together with 14% of the *altro*-regiomers resulting from the attack at C₃ of the epoxide (*cf. ref. 5*). Hydrogenation of **4** followed by isomerization of the alcohol **5** by an oxidation-reduction sequence afforded **6**⁶ which was converted into the acyclic derivative **7** by mercaptolysis and selective protection of the hydroxyl groups (*cf. ref. 7*). Desulfurization of the dithioacetal **7** with Raney nickel⁸ followed by the usual functional group manipulations provided the iodide **8**. Treatment of the latter with a higher order cuprate, generated from Me₂CuLi-LiCN + 2 eq (*E*)-Bu₃SnCH=CHSnBu₃,⁹ and then with an excess of N-iodosuccinimide afforded the desired (*E*)-vinyl iodide **9**, albeit in moderate yield. Stereospecific attaching of the (*Z*)-acrylamide unit was accomplished by Pd-catalyzed cross-coupling¹⁰ of iodide **9** with (*Z*)-Bu₃SnCH=CHCONH₂¹¹ to give the synthetic acetone derivative **10** [mp 99-100.5°C, [α]_D +22.5 (c 0.75, CHCl₃)], identical by ¹H- and ¹³C-NMR spectra to that obtained from the naturally occurring antibiotic.² Hydrolysis of the acetone moiety, temporary protection of the less hindered hydroxy-group at C₇ as a triethylsilyl ether, acylation of the other hydroxyl at C₉ and final desilylation, performed without purification of the intermediates, furnished the (7*R*, 8*R*, 9*S*, 10*R*) isomer **1** in a 46% non-optimized yield together with the regiomeric cinnamate (14%) and the corresponding diol which could be recycled.

The synthetic product **1** was found to be identical with the antibiotic YM-47522 by NMR spectroscopy but possessing the opposite sign of optical rotation.² Hence, the absolute configuration of the naturally occurring antibiotic YM-47522 is (7*S*, 8*S*, 9*R*, 10*S*), as shown on the Scheme.



a. $(\text{CH}_2=\text{CHCH}_2)_2\text{Mg}/\text{Et}_2\text{O}$, Δ , 0.5 h; b. H_2 , Pd/C/MeOH; c. NMO- Pr_4NRuO_4 (0.02 eq), MS 4Å/MeCN, rt, 0.5 h; d. NaBH_4 - $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}/\text{MeOH}$, -20°C , 0.5 h; e. $\text{HSCH}_2\text{CH}_2\text{SH}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$, rt, 2 h; f. $\text{Ac}_2\text{O}/\text{Py}$, -10°C , 2 h; g. $\text{Me}_2\text{CO}-\text{Me}_2\text{C}(\text{OMe})_2$, TsOH (cat); h. Ra-Ni/EtOH, Δ , 0.5 h; i. $\text{K}_2\text{CO}_3/\text{MeOH}$, rt, 0.5 h; j. TsCl/Py; k. LiI-HMPA/PhMe, Δ , 0.5 h; l. $\text{Me}_2\text{CuLi-LiCN}$, 2 eq (*E*)- $\text{Bu}_3\text{SnCH}=\text{CHSnBu}_3/\text{THF-Et}_2\text{O}$, rt, 2 h, then +8, -78°C to rt, then NIS, rt; m. (*Z*)- $\text{Bu}_3\text{SnCH}=\text{CHCONH}_2$, $(\text{MeCN})_2\text{PdCl}_2$ (0.05 eq)/DMF, rt, 24 h; n. AcOH- H_2O (4:1), 60°C , 6 h; o. 1.2 eq $\text{Et}_3\text{SiCl}/\text{Py}$, 0°C , then $\text{PhCH}=\text{CHCOCl}$, DMAP/ CH_2Cl_2 , rt; p. HF (aq)-MeCN, rt, 1 h.

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