Pergamon

*Tetrahedron Letters*, Vol. 37, No. 37, pp. 6711-6712, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01466-9

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

**Mikhail S. Ermolenko**

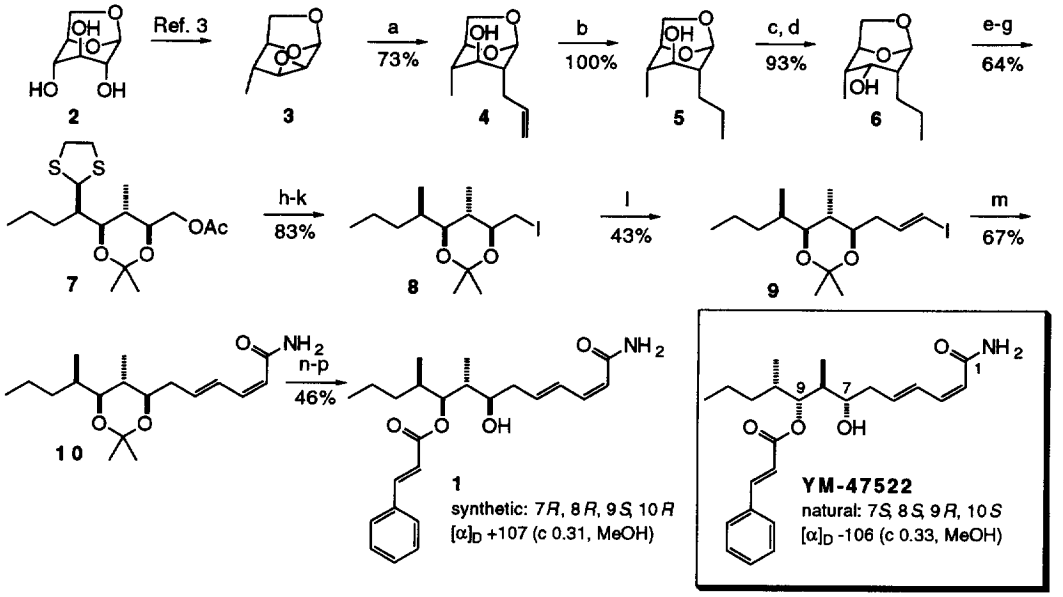
Institut de Chimie des Substances Naturelles du C.N.R.S., 91198 Gif-sur-Yvette, France

***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 (7S, 8S, 9R, 10S).*


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 diallylmagnesium[4] proceeded mainly at $C_2$ to give the *gluco*-alcohol **4** together with 14% of the *altro*-regiomer resulting from the attack at $C_3$ 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 nickel[8] followed by the usual functional group manipulations provided the iodide **8**. Treatment of the latter with a higher order cuprate, generated from $Me_2CuLi{\cdot}LiCN$ + 2 eq (*E*)-$Bu_3SnCH{=}CHSnBu_3$,[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-coupling[10] of iodide **9** with (*Z*)-$Bu_3SnCH{=}CHCONH_2$[11] to give the synthetic acetonide derivative **10** {mp 99-100.5°C, $[\alpha]_D$ +22.5 (c 0.75, $CHCl_3$)}, identical by $^1H$- and $^{13}C$-NMR spectra to that obtained from the naturally occurring antibiotic.[2] Hydrolysis of the acetonide moiety, temporary protection of the less hindered hydroxy-group at $C_7$ as a triethylsilyl ether, acylation of the other hydroxyl at $C_9$ 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. $(CH_2{=}CHCH_2)_2Mg/Et_2O$, 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. $NaBH_4$-$CeCl_3{\cdot}7\ H_2O$/MeOH, -20°C, 0.5 h; e. $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O/CH_2Cl_2$, rt, 2 h; f. $Ac_2O$/Py, -10°C, 2 h; g. $Me_2CO$-$Me_2C(OMe)_2$, TsOH (cat); h. Ra-Ni/EtOH, Δ, 0.5 h; i. $K_2CO_3$/MeOH, rt, 0.5 h; j. TsCl/Py; k. LiI-HMPA/PhMe, Δ, 0.5 h; l. $Me_2CuLi{\cdot}LiCN$, 2 eq (*E*)-$Bu_3SnCH{=}CHSnBu_3$/THF-$Et_2O$, rt, 2 h, then +**8**, -78°C to rt, then NIS, rt; m. (*Z*)-$Bu_3SnCH{=}CHCONH_2$, $(MeCN)_2PdCl_2$ (0.05 eq)/DMF, rt, 24 h; n. AcOH-$H_2O$ (4:1), 60°C, 6 h; o. 1.2 eq $Et_3SiCl$/Py, 0°C, then PhCH=CHCOCl, DMAP/$CH_2Cl_2$, rt; p. HF (aq)-MeCN, rt, 1 h.

## *References and Notes*


1. Shibazaki, M.; Sugawara, T.; Nagai, K.; Shimizu, Y.; Yamaguchi, H.; Suzuki, K. *J. Antibiotics* **1996**, *49*, 340-344.
2. Sugawara, T.; Shibazaki, M.; Nakahara, H.; Suzuki, K. *J. Antibiotics* **1996**, *49*, 345-348.
3. Sviridov, A. F.; Berdimbetova, G. E.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 2572-2574.
4. Ermolenko, M. S.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.* **1994**, *35*, 711-714.
5. (a) Sviridov, A. F.; Yashunsky, D. V.; Ermolenko, M. S.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 723-725; (b) Nakamura, H.; Arata, K.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2435-2441.
6. Product **6** contained ca. 5% of the isomer **5** which was separated out later along the scheme.
7. Kochetkov, N. K.; Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S. *Tetrahedron* **1989**, *45*, 5109-5136.
8. Prepared according to Burgstahler's procedure (Fieser, L. M.; Fieser, M. *Reagents for organic synthesis*, vol. 1; John Willey: New York, 1967; p. 729), commercial Ra-Ni is low reactive in this desulfurization.
9. Behlin, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Amer. Chem. Soc.* **1988**, *110*, 2641-2643.
10. Stille, J. K.; Groh, B. L. *J. Amer. Chem. Soc.* **1987**, *109*, 813-817.
11. Prepared in 78% yield by the treatment of the known[10] (*Z*)-$Bu_3SnCH{=}CHCO_2Et$ with $Me_2AlNH_2$.[12]
12. Basha, A.; Lipton, M.; Weinreb, M. *Tetrahedron Lett.* **1977**, 4171-4174; see also: Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1238-1240.


(*Received in France* 7 *July* 1996; *accepted* 23 *July* 1996)