

First Total Synthesis of the Antitumor Antibiotic (±) -Resorthiomycin

Datta E. Ponde, S. Ramalingam, Mahesh L. Patil, Hanumant B. Borate and
Vishnu H. Deshpande*

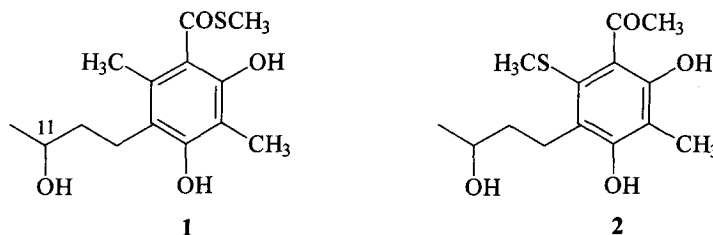
Division of Organic Chemistry : Technology, National Chemical Laboratory, Pune 411 008, India

Received 26 March 1999; accepted 19 May 1999

Abstract: The first total synthesis of (±)-resorthiomycin, an antitumor antibiotic has been achieved.
© 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Resorthiomycin, antibiotic, antitumor, thiol ester.

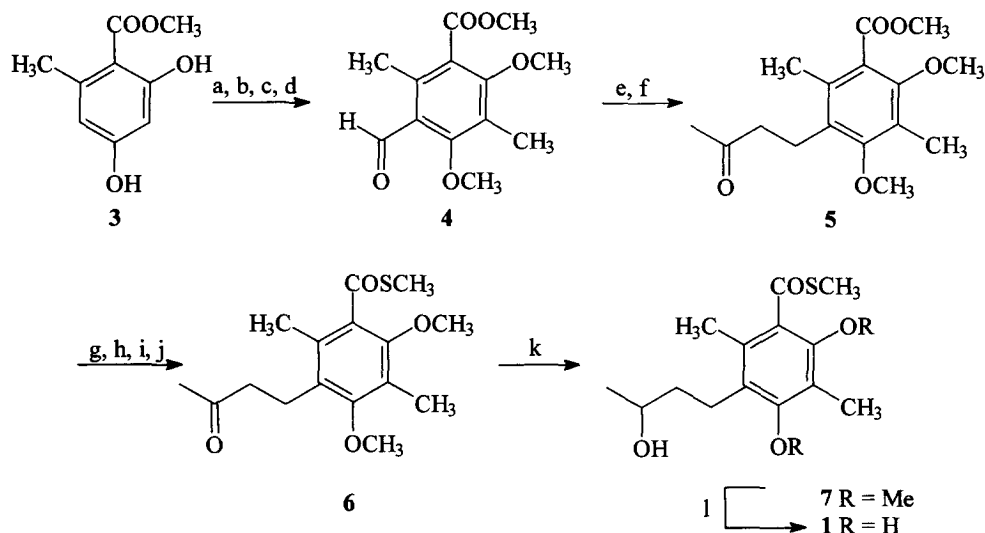
Resorthiomycin (**1**) is an antitumor antibiotic isolated¹ from the culture broth of *Streptomyces collinus* 45H-6. Its originally proposed structure **2**² was revised later on the basis of spectral data and an ester exchange reaction.³ However the absolute configuration at C-11 has not been determined. Besides having antitumor activity it also enhances anticancer activity of vincristine and actinomycin D.⁴ Although hexasubstituted benzene ring compounds are known in literature,⁵ substituted benzenecarbothioic acid methyl esters are rare entities. Very few methods are known for the preparation of methyl esters of carbothioic acids.⁶ The biological activity exhibited by resorthiomycin and the presence of an S-methyl ester in its structure prompted us to undertake the synthesis of resorthiomycin and in this communication we wish to report the first total synthesis of (±) - resorthiomycin (**1**).



The synthetic sequence used to prepare resorthiomycin is shown in Scheme I. Methyl 6-methyl-β-resorcyate (**3**) was prepared by a known method⁷ and subjected to successive Gattermann formylation, reduction,⁸ Duff formylation⁹ and methylation to obtain the aldehyde **4**. Condensation¹⁰ of the aldehyde **4** with acetone in presence of sodium hydroxide followed by selective reduction with magnesium in methanol¹¹ afforded the ketone **5**. The O-methyl ester functionality in **5** was transformed into an S-methyl ester by sequential hydrolysis, acid chloride formation, reaction with potassium hydrogen sulfide and methylation to afford the desired S-methyl ester **6**, the structure of which was confirmed by spectral data.¹²

Reduction of the ketone functionality in **6** with sodium borohydride provided resorathiomycin dimethyl ether **7**¹³ which on demethylation with aluminium chloride afforded (\pm)-resorathiomycin (**1**) having spectral features identical to those reported in the literature.³

Scheme I



a) $\text{Zn}(\text{CN})_2$, AlCl_3 , ether, 80%; b) $\text{Zn}(\text{Hg})$, HCl , MeOH , 78%; c) Hexamethylenetetramine, CF_3COOH , 90%; d) DMS , K_2CO_3 , acetone, 89%; e) acetone, NaOH , 71%; f) Mg , MeOH , 88%; g) KOH , MeOH , H_2O , 79%; h) SOCl_2 , benzene; i) KSH , H^+ , benzene; j) DMS , K_2CO_3 , acetone; k) NaBH_4 , MeOH , 90%; l) AlCl_3 , CH_2Cl_2 , 60%.

Acknowledgement: DEP and MLP thank CSIR, New Delhi for the award of senior research fellowship.

References and notes:

- Suzuki, H.; Tahara, M.; Takahashi, M.; Matsumura, F.; Okabe, T.; Shimazu, A.; Hirata, A.; Yamaki, H.; Yamaguchi, H.; Tanaka, N. and Nishimura, T. *J. Antibiotics*, **1990**, *43*, 129-134.
- Tahara, M.; Okabe, T.; Furihata, K.; Tanaka, N.; Yamaguchi, H.; Nishimura, T. and Suzuki, H. *J. Antibiotics*, **1990**, *43*, 135-137.
- Tahara, M.; Okabe, T.; Furihata, K.; Tanaka, N.; Yamaguchi, H.; Nishimura, T. and Suzuki, H. *J. Antibiotics*, **1991**, *44*, 255.
- Tahara, M.; Tomida, A.; Nishimura, T.; Yamaguchi, H. and Suzuki, H. *J. Antibiotics*, **1990**, *43*, 138-142.
- Gunzinger, J. and Tabacchi, R. *Helv. Chem. Acta.*, **1985**, *68*, 1936-1939 and 1940-1947.
- Ralston, A. W.; Segebrecht, E. W. and Bauer, S. T. *J. Org. Chem.*, **1939**, *4*, 502-505.
- Santesson, J. *Acta. Chem. Scand.*, **1970**, *24*, 3373-3378.
- Whalley, W. B. *J. Chem. Soc.*, **1949**, 3278-3280.
- Pulgarin, C.; Gunzinger, J. and Tabacchi, R. *Helv. Chem. Acta.*, **1985**, *68*, 1948-51.
- Porter, W. R. and Trager, W. F. *J. Hetero. Chem.*, **1977**, *14*, 319-320.
- Hudlicky, T.; Zingde, G. S. and Natchus, M. G. *Tetrahedron Lett.*, **1987**, *28*, 5287-5290.
- Compound **6**: IR (CHCl_3 , cm^{-1}): 1490, 1600, 1670 and 1710. PMR (200 MHz, CDCl_3): δ 2.18 (s, 3H); 2.19 (s, 3H); 2.20 (s, 3H); 2.48 (s, 3H); 2.55-2.65 (m, 2H); 2.80-2.92 (m, 2H); 3.72 (s, 6H, 2 \times OMe). MS (m/z): 310 (M^+ , 38%); 278 (10); 265 (58); 237 (22); 205 (38); 193 (100); 175 (18); 91 (25).
- Compound **7**: IR (CHCl_3 , cm^{-1}): 1570, 1673, 2928 and 3447. PMR (200 MHz, CDCl_3): δ 1.15 (d, $J=7$ Hz, 3H); 1.52-1.68 (m, 2H); 2.20 (s, 6H); 2.48 (s, 3H); 2.68-2.78 (m, 2H); 3.60-3.70 (m, 1H); 3.72 (s, 6H, 2 \times OMe). MS (m/z): 312 (M^+ , 5%); 265 (9); 138 (7); 120 (7); 107 (92); 91 (59); 77 (100); 65 (15).