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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

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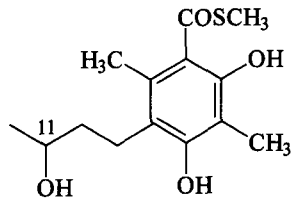
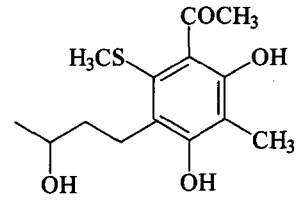
Abstract: The first total synthesis of (±)-resorthiomycin, an antitumor antibiotic has been achieved.

Keywords: Resorthiomycin, antibiotic, antitumor, thiol ester.

Resorthiomycin (**1**) is an antitumor antibiotic isolated[1] 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**).



1



2

The synthetic sequence used to prepare resorthiomycin is shown in Scheme I. Methyl 6-methyl-β-resorcylate (**3**) was prepared by a known method[7] and subjected to successive Gattermann formylation, reduction,[8] Duff formylation[9] and methylation to obtain the aldehyde **4**. Condensation[10] of the aldehyde **4** with acetone in presence of sodium hydroxide followed by selective reduction with magnesium in methanol[11] 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]

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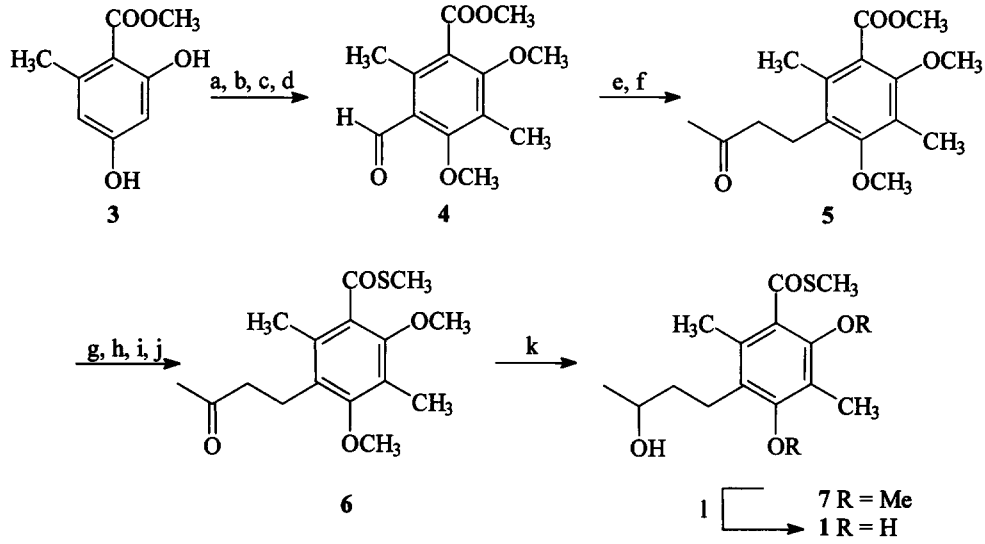
Reduction of the ketone functionality in **6** with sodium borohydride provided resorthiomycin dimethyl ether **7**[13] which on demethylation with aluminium chloride afforded (±)-resorthiomycin (**1**) having spectral features identical to those reported in the literature.[3]

Scheme I



a) Zn $(CN)_2$, $AlCl_3$, ether, 80%; b) Zn (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%.

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References and notes:

1) 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.

2) Tahara, M.; Okabe, T.; Furihata, K.; Tanaka, N.; Yamaguchi, H.; Nishimura, T. and Suzuki, H. *J. Antibiotics*, **1990**, *43*, 135-137.

3) Tahara, M.; Okabe, T.; Furihata, K.; Tanaka, N.; Yamaguchi, H.; Nishimura, T. and Suzuki, H. *J. Antibiotics*, **1991**, *44*, 255.

4) Tahara, M.; Tomida, A.; Nishimura, T.; Yamaguchi, H. and Suzuki, H. *J. Antibiotics*, **1990**, *43*, 138-142.

5) Gunzinger, J. and Tabacchi, R. *Helv. Chem. Acta.*, **1985**, *68*, 1936-1939 and 1940-1947.

6) Ralston, A. W.; Segebrecht, E. W. and Bauer, S. T. *J. Org. Chem.*, **1939**, *4*, 502-505.

7) Santesson, J. *Acta. Chem. Scand.*, **1970**, *24*, 3373-3378.

8) Whalley, W. B. *J. Chem. Soc.*, **1949**, 3278-3280.

9) Pulgarin, C.; Gunzinger, J. and Tabacchi, R. *Helv. Chem. Acta.*, **1985**, *68*, 1948-51.

10) Porter, W. R. and Trager, W. F.*J. Hetero. Chem.*, **1977**, *14*, 319-320.

11) Hudlicky, T; Zingde, G. S. and Natchus, M. G. *Tetrahedron Lett.*, **1987**, *28*, 5287-5290.

12) 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×OMe). MS (m/z): 310 (M^+, 38%); 278 (10); 265 (58); 237 (22); 205 (38); 193 (100); 175 (18); 91 (25).

13) 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×OMe). MS (m/z): 312 (M^+ ,5%); 265 (9); 138 (7); 120 (7); 107 (92); 91 (59); 77 (100); 65 (15).