A Total Synthesis of Methylenomycin B

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A new synthesis of methylenomycin B (**3**) has been accomplished in four steps starting with the reaction of methyl (*E*)-3-lithio-2-methyl-3-phenylthioprop-2-enoate (**2**) with ethyl 2-(phenylthiomethyl)prop-2-enoate (**4**).

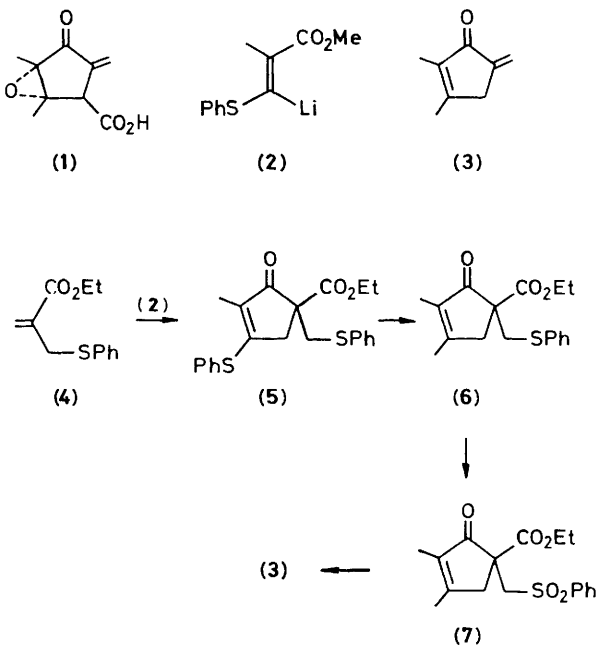
In a previous communication,[1] we described a total synthesis of (±)-methylenomycin A (**1**) using the cyclisation reaction between the vinyl-lithium reagent (**2**) and methyl acrylate as the key step.[2] In this paper we report a four step synthesis of the related antibiotic, methylenomycin B (**3**),[3,4] starting from (**2**) (Scheme 1).

The reaction of (**2**)[5] with the acrylate derivative (**4**)† at −80 °C for 1 h gave the cyclisation product (**5**) (m.p. 90.5—92 °C) in 63% yield [based on (**4**)];‡ i.r. ν_{max} ($CHCl_3$) 1735, 1695, and 1585 cm^{-1}; ^1H n.m.r. δ (CCl_4) 1.20 (3 H, t, *J* 7 Hz), 1.71 (3 H, t, *J* 2 Hz), 2.35 and 2.80 (each 1H, dq, *J* 11 and 2 Hz), 3.26 and 3.42 (each 1 H, AB type q, *J* 14 Hz), 4.07 (2 H, q, *J* 7 Hz), and 7.20 and 7.40 (each 5 H, br.). Treatment of (**5**) with 1 mol. equiv. of Me_2CuLi in a large amount of ether (−50 °C, 2—3 min)§ yielded the dimethyl enone (**6**) in 79%

† Prepared by the reaction of ethyl β,β′-dibromoisobutyrate with thiophenol (1 mol. equiv.) and triethylamine (2 mol. equiv.) (M. Kitaoka, H. Kosugi, and H. Uda, unpublished results). The free acid is known (G. K. Pajagopalan and S. Swaminathan, *Synthesis*, 1976, 409).

‡ Yields are for the isolated pure products. Satisfactory analytical data have been obtained for all new compounds.

§ Quenching the reaction with aqueous ammonium chloride immediately after the addition of Me_2CuLi is essential for optimum yield. A long reaction time caused the formation of the saturated trimethyl ketone.



Scheme 1

yield; i.r. ν_{max} ($CHCl_3$) 1735, 1705, and 1650 cm^{-1}; ^1H n.m.r. δ (CCl_4) 1.22 (3 H, t, *J* 7 Hz), 1.65 (3 H, br.s), 2.07 (3 H, br.s), 2.50 and 3.06 (each 1H, br.d, *J* 14 Hz), 3.21 and 3.56 (each 1 H, AB type q, *J* 12 Hz), 4.08 (2 H, q, *J* 7 Hz), and 7.10—7.40 (5 H, m).

Removal of the ethoxycarbonyl group and the formation of the α-methylene functionality and thus completion of the total synthesis were achieved *via* the sulphone compound (**7**). This was prepared in 93% yield by treating (**6**) with 2 mol. equiv. of *m*-chloroperbenzoic acid in CH_2Cl_2 at 0 °C for 1 h. Exposure of (**7**) to aqueous NaOH (2 mol. equiv.)–Me_2SO (0 °C to room temperature) for 1 h gave directly *via* hydrolysis, decarboxylation, and the elimination of sulphinic acid, methylenomycin B (**3**) in 44% yield;¶ i.r. ν_{max} ($CHCl_3$) 1690, 1660, 1635 (sh.), and 1625 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1.77 (3 H, br.s), 2.08 (3 H, br.s), 3.10 (2 H, br.s), 5.40 (1 H, t, *J ca.* 2 Hz), and 6.03 (1 H, t, *J* 2.5 Hz), consistent with the reported values.[3,4]

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¶ An attempt to convert (**6**) into (**3**) was unsatisfactory; the major product (48%) was 2,3-dimethyl-5-(phenylthiomethyl)cyclopent-2-enone. The low yield of (**3**) may be due to its instability.