A Total Synthesis of (±)-Methylenomycin A

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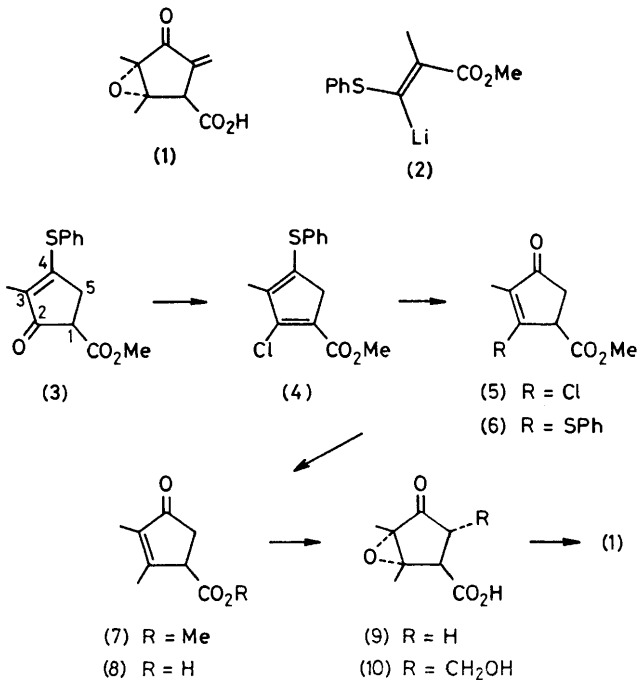
Summary A new synthesis of (±)-methylenomycin A (**1**) has been accomplished by applying the cyclisation reaction between the vinyl-lithium reagent (**2**) and methyl acrylate as the key step.

IN connection with our synthetic studies using the vinyl-lithium reagents generated from 3-heteroatom-functionalised propenoic acid derivatives,[1] we found that in the reaction with $\alpha\beta$-enoates the vinyl-lithium reagent (**2**) underwent Michael addition and subsequent Dieckmann cyclisation to afford functionalised cyclopentenone derivatives in one step.[1a] We report here a total synthesis of (±)-methylenomycin A,[2,3] one of the cyclopentanoid antibiotics produced by *Streptomyces violaceoluber*, by a route which involves the new cyclisation reaction as the key skeleton-forming step (Scheme).



SCHEME

The key intermediate (**3**), m.p. 69—71·5 °C, was prepared in 83% yield (based on methyl acrylate) or 42% from (**2**) from the reaction between the vinyl-lithium reagent (**2**), generated from methyl (*E*)-2-methyl-3-phenylthioprop-2-enoate by the action of lithium di-isopropylamide (LDA), and methyl acrylate according to the procedure previously reported[1a] except that we used a different ratio of (**2**) to methyl acrylate.†

The ketone transposition from C-2 in (**3**) to C-4 and the introduction of a methyl group at C-2 were achieved as follows.‡ Treatment of (**3**) with 3 mol. equiv. of PCl_3 in refluxing chloroform (48 h) yielded the diene chloride (**4**),§ m.p. 62—63·5 °C, in 84% yield. Compound (**4**), (8 mmol) was hydrolysed using $TiCl_4$ (2 mol. equiv., 0 °C for 0·5 h) in CH_2Cl_2–acetic acid (1 : 1; 150 ml) and then by addition of H_2O (4 mol. equiv., 16 h at room temperature)[4] to give the chloride (**5**) (76% yield) together with a small amount of the rearranged sulphide (**6**);¶ for (**5**): ^{1}H n.m.r. δ (CCl_4) 1·80 (3 H, d, *J* 2·0 Hz), 2·67 (2 H, d, *J* 6·0 Hz), and 3·77 (OMe overlapped with 1 H multiplet); for (**6**): δ (CCl_4) 1·80 (3 H, d, *J* 2·0 Hz), 2·18 (1 H, dd, *J* 18·0 and 1·5 Hz), 2·68 (1 H, dd, *J* 18·0 and 3·5 Hz), 3·40 (OMe), 3·67 (1 H, m), and 7·39 (5 H). The formation of the sulphide (**6**) was confirmed by the fact that (**5**), when treated with PhSH in a mixture of CH_2Cl_2 and acetic acid containing $TiCl_4$, afforded (**6**) in high yield.

Both (**5**) and (**6**) were then treated with Me_2CuLi (−65 °C, 2 h) to give the same methylated enone (**7**) in 60% and 70% yield, respectively; ^{1}H n.m.r. δ (CCl_4) 1·70 (3 H, br. s), 2·03 (3H, br. s), 2·50 (2 H, d, *J* 6·0 Hz), 3·57 (1 H, m), and 3·70 (OMe); i.r. ν_{max} 1740, 1710, and 1650 cm^{-1}. Saponification of (**7**) under alkaline conditions (2 mol. equiv. of NaOH, aq. MeOH, 1 h at 0 °C) gave the free acid (**8**) [81% yield, m.p. 82·5—84·5 °C (decomp.) (lit.,[3b] 81—83 °C)]. The acid (**8**) was converted upon treatment with 30% H_2O_2 under alkaline conditions into the *trans* epoxy-acid (**9**) [m.p. 125·5—126·5 °C (lit.,[3b] 125·5—127 °C)] in 81% yield. The final reactions for the introduction of an α-methylene unit were carried out in a similar fashion to that described by Jernow *et al.*[3b] Treatment of (**9**) with LDA in tetrahydrofuran followed by addition of ethereal formaldehyde gave (**10**), dehydration of which gave (±)-methylenomycin A which was purified by column chromatography [40% from (**8**)] and was identical spectroscopically with the natural compound.

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† The use of an excess of (**2**) with respect to methyl acrylate (2 : 1 mol. ratio) is essential for optimising the yield because the resulting β-keto-ester in the reaction consumes the starting vinyl-lithium (**2**) to form the corresponding lithium enolate.

‡ Direct introduction of a methyl group on C-2 in (**3**) using methylmagnesium bromide or methyl-lithium was unsuccessful, resulting only in the formation of the enolate.

§ Satisfactory analytical and spectroscopic data have been obtained for all new compounds.

¶ The yield of (**6**) depends on the reaction conditions; higher concentrations of (**4**) (40 mmol/350 ml) increased the yield of (**6**) to 27%, with a yield of (**5**) of 50%.

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[2] For the structural elucidation of (**1**) see T. Haneishi, N. Kitahara, T. Takiguchi, M. Arai, and S. Sugawara, *J. Antibiot.*, 1974, **27**, 386; T. Haneishi, A. Terahara, T. Hata, and T. Tamura, *ibid.*, p. 393.

[3] For syntheses of (**1**) see (a) R. M. Scarborough and A. B. Smith, III, *J. Am. Chem. Soc.*, 1977, **99**, 7085; (b) J. Jernow, W. Tautz, P. Rosen, and J. F. Blout, *J. Org. Chem.*, 1979, **44**, 4210; (c) M. Koreeda, Y. P. Liang Chen, and H. Akagi, 178th Natl. Am. Chem. Soc. Meeting, Washington, D.C., U.S.A., 1979 and personal communication from Prof. M. Koreeda; (d) R. M. Scarborough, B. H. Toder, and A. B. Smith, III, *J. Am. Chem. Soc.*, 1980, **102**, 3904.

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