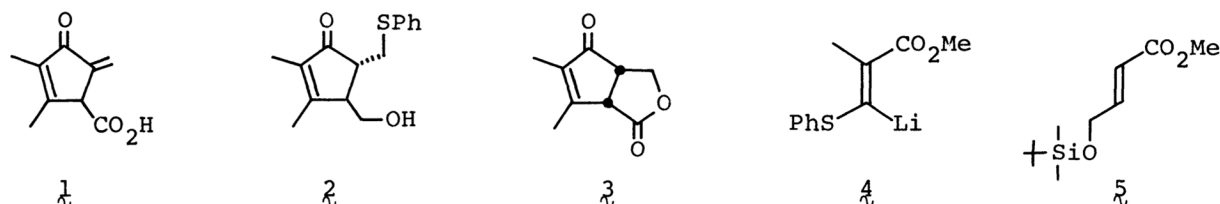


SYNTHESIS OF (\pm)-DESEPOXY-4,5-DIDEHYDROMETHYLENOMYCIN A

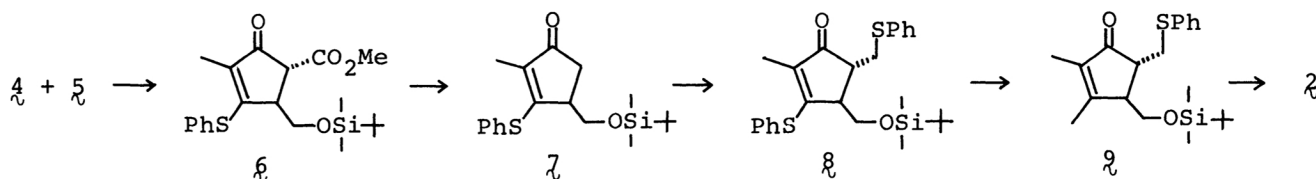
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The reaction of methyl (E)-3-lithio-2-methyl-3-phenylthioprop-2-enoate (**4**) with methyl (E)-4-(t-butyldimethylsilyloxy)but-2-enoate (**5**) provides the functionalized cyclopentenone (**6**) in one step, which is transformed into both Koreeda's and Smith's intermediates (**7**) and (**3**) for synthesis of (\pm)-desepoxy-4,5-didehydromethylenomycin A (**1**).

Recently, two total syntheses ^{1,2)} of (\pm)-desepoxy-4,5-didehydromethylenomycin A (**1**), an unstable cyclopentenoid antibiotic isolated from Streptomyces coelicolor A3(2), ³⁾ have been reported, in which compounds (**2**)¹⁾ and (**3**)²⁾ have been employed as the key intermediates for completion of the syntheses, respectively. In connection with the synthetic studies applying a cyclopentenone annulation reaction with the vinyl-lithium reagent (**4**)⁴⁾ we found that the annulation product (**6**) derived from the reaction with the acrylate derivative (**5**) was the versatile precursor for the preparation of both Koreeda's (**2**) and Smith's intermediates (**3**).

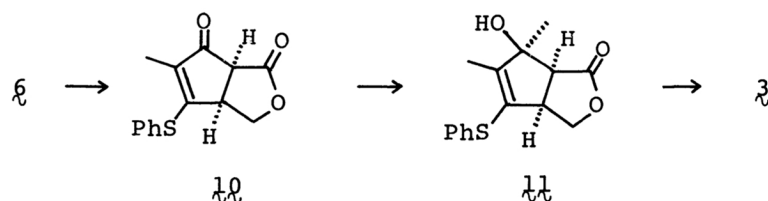


The reaction of (**4**)^{4a)} with the silyl ether (**5**) of hydroxybutenoate⁵⁾ (0.5 mol. equiv., inverse addition, -50~0 °C for 2 h, then 0 °C for 15 h) gave the annulated product (**6**) in 70% yield [based on (**5**)].⁶⁾ Upon treatment with NaCl (1.2 mol. equiv.) in dimethyl sulfoxide containing water (2 mol. equiv.) (115 °C, 5 h), compound (**6**) produced directly the decarboxylated product (**7**) in 88% yield. Treatment of (**7**) first with lithium hexamethyldisilazide (1.2 mol. equiv.) in tetrahydrofuran and then with iodomethyl phenyl sulfide (2 mol. equiv., -76~40 °C, 4 h) afforded in 50% yield the 5-phenylthiomethylated compound (**8**), mp 93~94 °C. The introduction of an additional methyl group and thus transformation into the intermediate (**2**) were



achieved by a conjugate addition of organo copper reagent followed by hydrolysis. Thus, compound (8) was treated with Me_2CuLi (2 mol. equiv., -35°C , 2 h) in ether to give the 3-methyl-exchanged compound (9), which gave in 78% yield from (8) the Koreeda's intermediate (2), identical with the authentic sample, by hydrolysis with aqueous HF in acetonitrile (room temp., 1.5 h).

Compound (6) could be also converted into the Smith's intermediate (3) via only three steps. Treatment of (6) with concd. HBr (excess, room temp., 3 h) in acetic acid (for making a homogeneous solution) gave the lactone (10), mp $116\sim 117^\circ\text{C}$, in 90% yield. Easy lactonization, with concomitant epimerization of the ester function may be facilitated by the highly enolizable characteristic of (6). In contrast to



preferential deprotonation in the case of α -methoxycarbonyl analogues,^{1,4b)} this α -lactonic ketone moiety of (10) reacted smoothly with methyllithium (1.2 mol. equiv., $-78\sim -40^\circ\text{C}$, 2 h) to yield the precursor (11) in 65% yield. Hydrolysis of (11) in a mixture of trifluoroacetic acid and benzene (1:10 v/v, room temp., 3.5 h) furnished the 1,3-ketone transpositioned enone lactone (3), the Smith's intermediate, which was identical spectroscopically with the authentic compound. Thus, the present study represents completion of the formal total synthesis of (\pm)-desepoxy-4,5-didehydromethylenomycin A (1) via two alternative routes starting from the common precursor (6).

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References

- 1) M. Koreeda and Y. P. Liang Chen, *Tetrahedron Lett.*, **22**, 15 (1981).
- 2) D. Boschelli, R. M. Scarborough, Jr., and A. B. Smith, III, *Tetrahedron Lett.*, **22**, 19 (1981).
- 3) U. Hornemann and D. A. Hopwood, *Tetrahedron Lett.*, 2977 (1978).
- 4) (a) K. Isobe, M. Fuse, H. Kosugi, H. Hagiwara, and H. Uda, *Chem. Lett.*, **1979**, 785; (b) Y. Takahashi, K. Isobe, H. Hagiwara, H. Kosugi, and H. Uda, *J. Chem. Soc., Chem. Commun.*, 714 (1981); (c) Y. Takahashi, H. Kosugi, and H. Uda, *ibid.*, in press.
- 5) R. Rambaud, *Bull. soc. chim. France*, [5] **1**, 1317 (1934).
- 6) Compound (6) was contaminated with a trace of chromatographically inseparable impurity. Yields of others are for the isolated pure products. All new compounds were characterized by combustion analysis (or mass spectroscopy) as well as by IR, UV, and ^1H NMR spectroscopy.

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