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Total Synthesis of (-)-Avenaciolide

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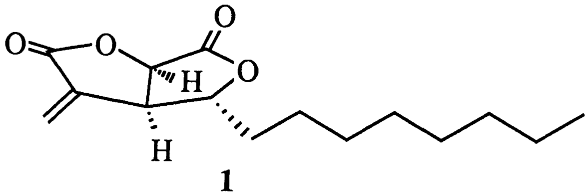
(-)-Avenaciolide **1** was synthesized highly stereoselectively in 7 steps from ethyl 3-chloro-4-oxododecanoate via the kinetic resolution of ethyl 4-acetoxy-3-chlorododecanoate by lipase-catalyzed hydrolysis.

Avenaciolide **1** is an antifungal agent first isolated from Aspergillus avenaceaus.[1] The unusual structure having α-methylene bis(butyrolactone) system has prompted a measure of synthetic activity resulting in the description of four total syntheses of the racemate.[2] Total synthesis of optically active avenaciolide starting from D-glucose via 11 steps has been reported by two groups.[3,4] Here we wish to report a facile and highly stereoselective synthesis of **1**. As shown in the scheme, the reaction sequence consists of 7 steps and contains the kinetic resolution of ethyl 4-acetoxy-3-chlorododecanoate (**4**) by lipase-catalyzed hydrolysis as a key step.



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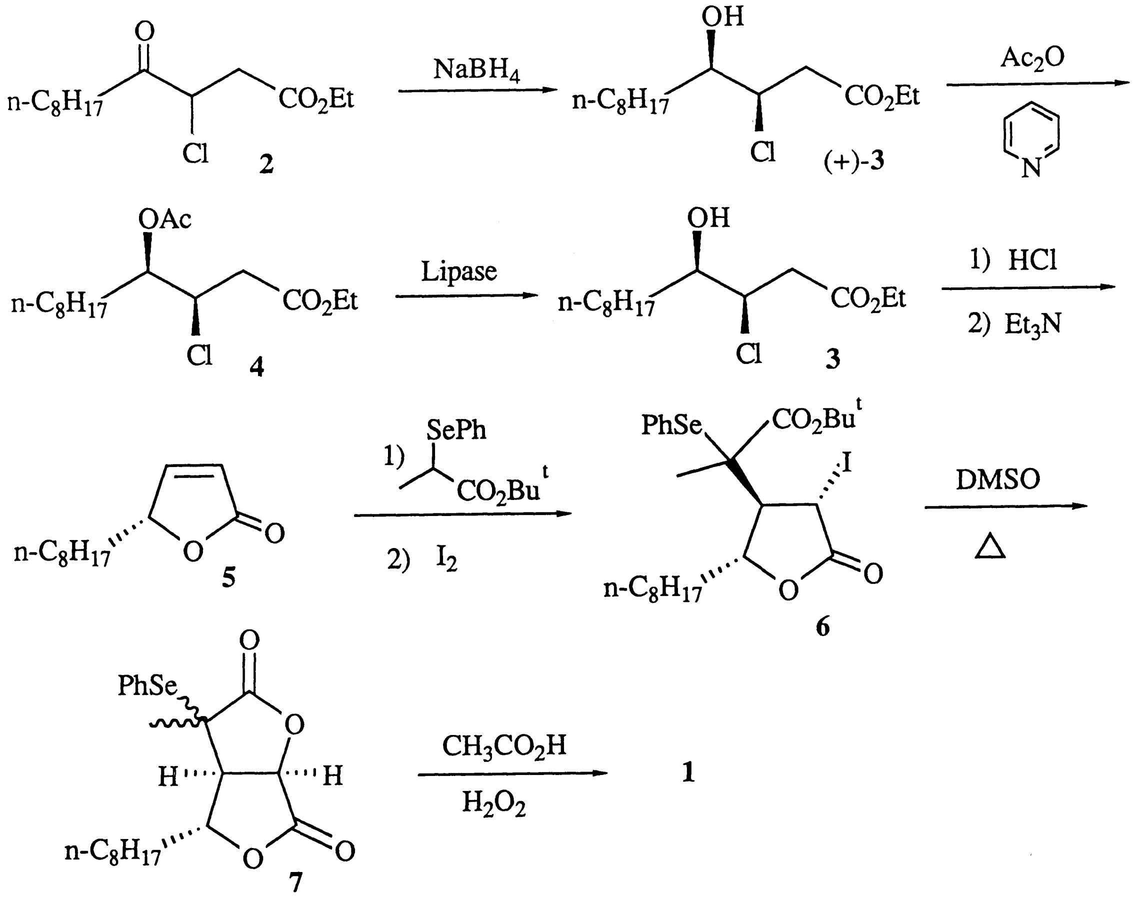
Reduction of ethyl 3-chloro-4-oxododecanoate (**2**)[5] with sodium borohydride (EtOH, 0 °C, 10 min) gave ethyl syn-3-chloro-4-hydroxydodecanoate [(+)-**3**][6] in 73% yield with high stereoselectivity. Regioselective hydrolysis of the corresponding acetate **4** with lipase (Amano P)(25 °C, 40 h) afforded optically active **3** in 31% yield with 94% ee. Hydrolysis (HCl, 25 °C, 21 h) and the subsequent dehydrochlorination with triethylamine (ether, 25 °C, 36 h) gave (5R)-5-octyl-2(5H)furanone (**5**) in 59% yield with 94% ee.[7] The conversion of **5** to **1** was successfully established by modifying the procedure developed by Schlessinger, et al.[2b,c]

Michael addition of the anion of t-butyl 2-selenophenylpropionate (LDA, THF, -78 °C, 3 h) to **5** and the subsequent iodonation afforded the trans-addition product **6** in 89% as a single product. Thermal treatment of **6** in dimethyl sulfoxide (140 °C, 15 min) gave selenophenyl bislactone **7** in 47% yield. Oxidation of **7** with peracetic acid (THF, 0-25 °C, 1 h) gave (-)-avenaciolide **1**[9] in 31% yield, accompanied by the simultaneous elimination of a phenylselenoxide group. Spectral data of the product **1** obtained here were identical with those of an authentic sample.[2]

The present synthesis provides **1** in moderate yields with high stereoselectivity in the all steps. Experimental details of the syntheses of **1** and optically active



butenolides will be reported in due course.

References

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2) W. L. Parker and F. Johnson, J. Org. Chem., 38, 2489 (1973); J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, J. Am. Chem. Soc., 95, 7923 (1973); J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, ibid., 101, 1544 (1979); H. Takei, Y. Fukuda, T. Taguchi, T. Kawara, H. Mizutani, and T. Mukuta, Chem. Lett., 1980, 1311.

3) H. Ohrui and S. Emoto, Tetrahedron Lett., 1975, 3657.

4) R. C. Anderson and B. Fraser-Reid, J. Am. Chem. Soc., 97, 3870 (1975).

5) Compound **2** was prepared in high yields by the alkylation of sodio t-butyl 3-oxoundecanoate with ethyl iodoacetate and the subsequent chlorination of the condensation product with sulfuryl chloride and the decarboxylation of the chlorinated diester with p-toluenesulfonic acid.

6) Syn geometry was determined by the NMR spectrum of **4** exhibitting the small coupling constant (J = 2.0 Hz) between C-3 and C-4 protons.

7) **5**: $[\alpha]^{25}_{D}$-64.9° (c 2.56, dioxane)(lit.$^{8)}$ -69.2° (c 2.0, dioxane)).

8) J. P. Vigneron and J. M. Blanchard, Tetrahedron Lett., 21, 1739 (1980).

9) Physical properties of **1**: mp 49-51 °C (lit.$^{4)}$ 50-51 °C); $[\alpha]^{23.5}_{D}$ -38° (c 0.47, EtOH)(lit.$^{4)}$ $[\alpha]^{26.5}_{D}$ -41.6° (c 1.27, EtOH)); 91% ee.

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