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A SHORT STEP SYNTHESIS OF FERRULACTONE I[1)]

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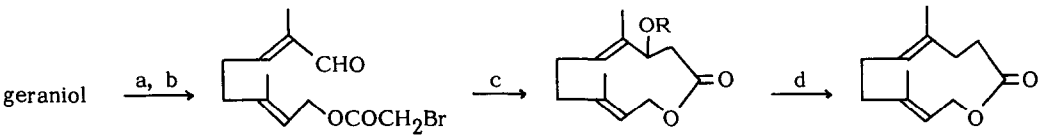
Summary: Ferrulactone I, a 11-membered macrolide insect pheromone, was synthesized straightforwardly from geraniol with the efficient use of two SmI_2-promoted reactions in the key steps; intramolecular Reformatsky reaction and a novel regioselective reduction of allylic benzoate.

While usual macrolide antibiotics have even-membered lactone structure, several macrocyclic lactones with odd-membered rings have recently been found in nature as insect pheromones.[2)] In this communication, we wish to describe an efficient synthesis of a 11-membered aggregate pheromone of grain beetles, Ferrulactone I (**3**).[3)]

Geraniol was converted into the ω-bromoacetoxy aldehyde (**1**) in 38% overall yield by the conventional procedures; bromoacetylation followed by allylic oxidation with catalytic SeO_2 supported on silica gel and t-butyl hydroperoxide.[4)]



1

2a : R = Ac
2b : R = Bz
2c : R = $COCO_2Me$

3

a) $BrCH_2COBr$, Et_3N. b) SeO_2 on SiO_2, TBHP. c) SmI_2-THF, 0°C; RCOCl, DMAP, RT.
d) SmI_2-THF-HMPA, pivalic acid, 0°C.

SmI_2-promoted cyclization of **1** followed by acylation of the resulting unstable β-hydroxydecadienolide with an appropriate acylating reagent in the same pot afforded the 11-membered lactone acetate (**2a**), benzoate (**2b**),[5)] and oxalate (**2c**) in 60%, 47%, and 20% yield, respectively.[6)] Subsequent selective allylic deacyloxylation of **2a**, **2b**, or **2c** was not so easy mainly because of the particular structure of the substrates in which the lactone oxygen also resides at the allylic position: Palladium-catalyzed reduction of **2a** or **2b** with SmI_2,[7)] triphenylsilane reduction of **2a**,[8)] or tributyltin hydride reduction of **2c**[9)] did not give satisfactory results. However, we found that the reduction of **2b** with SmI_2-THF-HMPA system[10)] in the presence of pivalic acid gave the pheromone (**3**) in 15% yield. The yield of this conversion could be much improved by devising the addition procedure, i.e., when a solution of **2b** and pivalic acid in THF was added dropwise to a solution of SmI_2 and HMPA in THF at 0°C over 30 min, smooth reaction took place and, after chromatographic purification, 78% yield of

3 was obtained as an oil.[11] In this reaction, neither the regioisomer nor the stereoisomer of the double bond was detected.[12,13]

Thus, 4-step synthesis of Ferrulactone I was accomplished with the efficient use of SmI_2.

We are grateful to Professor A. C. Oehlschlager, Simon Fraser University, for providing the ^1H NMR (400 MHz) spectrum of Ferrulactone I and useful informations about the spectral features of this compound.

References and Notes

1) Lanthanides in Organic Synthesis. 20. A part of this study was presented at the 55th National Meeting of the Chemical Society of Japan, Fukuoka, October, 1987.
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4) B. R. Chhabra, K. Hayano, T. Ohtsuka, H. Shirahama, and T. Matsumoto, Chem. Lett., 1703 (1981); M. A. Umbreit and K. B. Sharpless, J. Am. Chem. Soc., 99, 5526 (1977).
5) Colorless crystals: Mp 86-87 °C; Mass (m/z) 314 (M^+); ^1H NMR (400 MHz) $CDCl_3$ δ 1.71 (3H, s), 1.72 (3H, d, J=1.0 Hz), 2.0-2.3 (3H, m), 2.30-2.55 (1H, broad s), 2.7-2.8 (2H, m), 4.35-4.55 (1H, broad s), 4.60-4.75 (1H, broad s), 5.20-5.34 (1H, broad d), 5.50-5.62 (1H, broad t), 5.62-5.75 (1H, broad t), 7.43 (2H, t, J=7.81 Hz), 7.56 (1H, t, J=7.32 Hz), 7.95-8.15 (2H, broad d).
6) For a highly efficient method for the preparation of medium- and large-ring lactones by utilizing SmI_2-promoted intramolecular Reformatsky reaction, see T. Tabuchi, K. Kawamura, J. Inanaga, and M. Yamaguchi, Tetrahedron Lett., 27, 3889 (1986).
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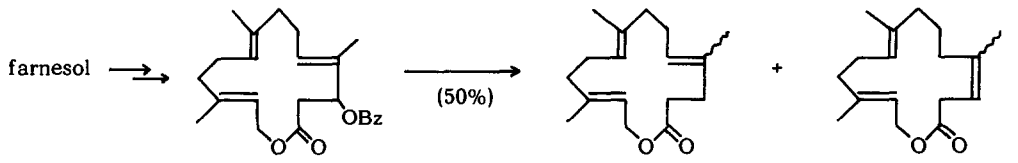
9) S. C. Dolan and J. MacMillan, J. Chem. Soc., Chem. Commun., 1588 (1985).
10) J. Inanaga, M. Ishikawa, and M. Yamaguchi, Chem. Lett., 1485 (1987); K. Otsubo, K. Kawamura, J. Inanaga, and M. Yamaguchi, ibid., 1487 (1987); K. Otsubo, J. Inanaga, and M. Yamaguchi, Tetrahedron Lett., 27, 5763 (1986).
11) Mass (m/z) 194 (M^+); ^1H NMR (400 MHz) spectrum of synthetic 3 was identical with the authentic one which was kindly provided by Prof. Oelschlager.
12) A double bond isomer, (3E,8E)-4,8-dimethyl-3,8-decadien-10-olide (suspensolide) is also an insect pheromone and has been synthesized very recently, see K. Mori and Y. Nakazono, Liebigs Ann. Chem., 167 (1988).
13) A 15-membered lactone benzoate (4) was also synthesized from farnesol in a similar manner to the preparation of 3. The reduction of 4 by the present method, however, produced a mixture of regio- and stereoisomers with respect to the C(4) double bond.



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