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GENERAL SYNTHESIS OF EXOMETHYLENE-γ-LACTONES VIA THE RETRO-DIELS-ALDER REACTION

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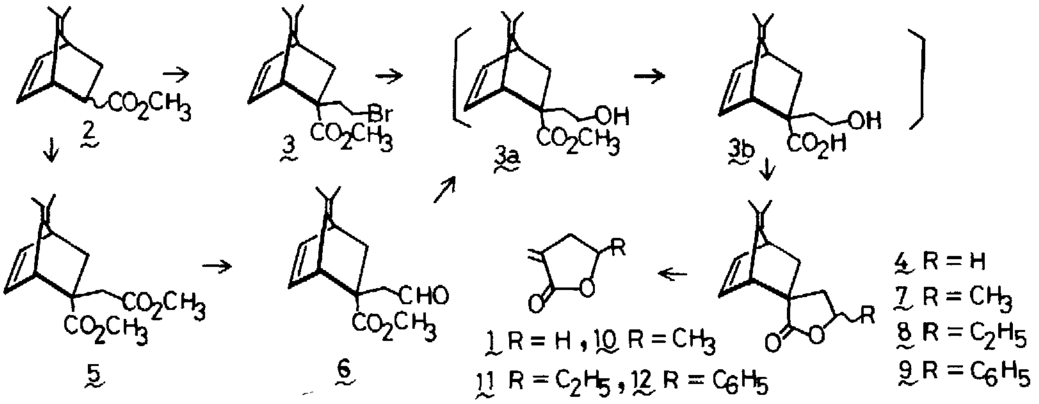
Summary. New synthetic methods of tulipalin A were deviced via the retro-Diels-Alder reaction and the generality was demonstrated by the synthesis of several α-methylene-γ-alkyl-γ-butyrolactones.

Previously, we have demonstrated the general synthesis of 2-alkyl-2-butenolactones via the retro-Diels-Alder reaction.$^{1)}$ We report herein a simple and general scheme for the synthesis of exomethylene-γ-alkyl-γ-butyrolactones via the retro-Diels-Alder reaction. The simplest congener, tulipalin A (1)$^{2)}$ which exerts antifungal and plant growth inhibitory activities$^{3)}$, was prepared by two methods as follows.$^{4)}$ The starting material, a methyl ester 2 was prepared according to previously reported procedure.$^{5)}$ Alkylation of the methyl ester 2 with ethylene dibromide in the presence of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) afforded a bromo ester 3$^{6)7)}$ in 74% yield. Treatment of the bromo ester 3 with 0.25N-NaOH in ethanol at refluxing and successive hydrolysis gave acidic product (3b), which was smoothly converted with p-toluenesulfonic acid in chloroform at room temperature into a lactone 4, white needles$^{8)}$, mp 97.2~97.3°C, in 63% yield. The same lactone 4 was prepared from a diester 5, which was obtained by alkylation of 2 with methyl bromoacetate according to the previously described procedure.$^{5)}$ Reduction of the diester 5 with diisobutylaluminium hydride in toluene at -50°C afforded selectively an aldehyde 6 in 50.4% yield. Reduction of 6 with sodium borohydride in THF at room temperature



followed by hydrolysis with 1% NaOH in dioxane at room temperature yielded the same acid 3b, which was transformed to 4 by the same way described above in 55% yield. The retro-Diels-Alder reaction of 4 in benzene heating at 140°C for 30 min in a sealed tube afforded tulipalin A (1) in 70% yield. Spectroscopic data of 1 were identical with those of reported sample.$^{2)}$ In order to confirm the generality of this method for the synthesis of exomethylene-γ-alkyl-γ-butyrolactones, the aldehyde 6 was alkylated with three other Grignard reagents (CH_3MgI, CH_3CH_2MgBr, C_6H_5MgBr) to yield the lactones (7,8,9) as a mixture of diastereomers in 50~54% yield. The reaction conditions of the pyrolysis, yields of products and their spectroscopic data are summarized in Table 1.

Table 1. The Retro-Diels-Alder Reaction of Lactones (4,7,8,9)

Compounds	reaction temp. (°C)	reaction time (min)	products (yield%)	IR (ν_{max})	^{1}H-NMR ($\delta^{CCl_4}_{TMS}$)
4 (mp97.2 ~97.3)	140	30	1 (70) (oil)	1765,1668 810	2.99(2H),4.36(2H) 5.64,6.13(2H)
7 (mp128.3 ~128.7)	140	30	10 (60) (oil)	1765,1668 810	1.44(3H),2.53(1H) 3.13(1H),4.62(1H) 5.56,6.11(2H)
8 (oil)	140	30	11 (54) (oil)	1770,1670 815	0.98(3H),1.61(2H) 2.44(1H),2.49(1H) 4.24(1H),5.34, 5.90(2H)
9 (oil)	140	30	12 (80) (mp55.5 ~55.8)	1760,1665 815	2.68(1H),3.24(1H) 5.26(1H),5.41, 5.99(2H),7.10(5H)

References and Notes

1) A. Ichihara, N. Nio, Y. Terayama, R. Kimura, S. Sakamura, Tetrahedron Letters, 3731 (1979). For other applications of natural products synthesis via the retro-Diels-Alder reaction, see: A. Ichihara, R. Kimura, S. Yamada, S. Sakamura, J. Am. Chem. Soc. in press.

2) R. Tschesche, F. J. Kammerer, G. Wulff, F. Schonbeck, Tetrahedron Letters, 701 (1968)

3) Y. Iino, A. Tanaka, K. Yamashita, Agric. Biol. Chem., 36, 2505 (1972)

4) For an excellent review on the synthesis of α-methylene lactones see: P. A. Grieco, Synthesis, 67 (1975)

5) R. Kimura, A. Ichihara, S. Sakamura, Synthesis, 516 (1979)

6) Satisfactory spectroscopic data (MS, IR, ^{1}H-NMR) were obtained for all new compounds.

7) The stereochemistry of 3 was deduced analogously from previous experiments.$^{5)}$

8) Satisfactory elemental analyses were obtained for all crystalline compounds.

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