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GENERAL ROUTE TO 2-ALKYL-2-BUTENOLACTONES VIA THE RETRO-DIELS-ALDER REACTION

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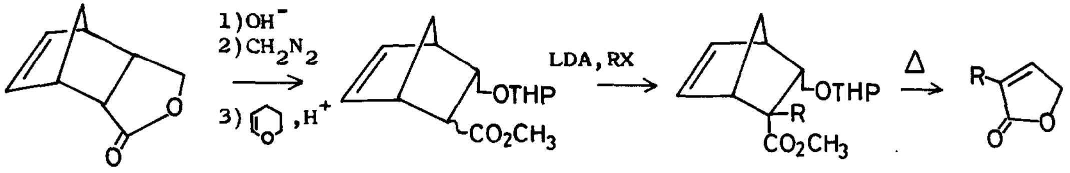
Summary. Various 2-alkyl-2-butenolactones were simply prepared from cyclopentadiene-maleic anhydride adducts through the retro-Diels-Alder reaction. The procedure was applied for the synthesis of dehydrolappaol A dimethyl ether.

In the previous paper[1)], we reported a facile synthesis of methyl 2-alkyl-2-alkenoates from methyl acrylate via the retro-Diels-Alder reaction. Present paper describes a new synthetic procedure of 2-alkyl-2-butenolactones,[2)] which would be useful intermediates for the syntheses of butyrolactone lignans[3)] such as hinokinin,[3a)] steganacin,[3b)] and lappaols.[3c)]

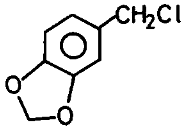
Reduction of the adduct from cyclopentadiene-maleic anhydride with sodium borohydride according to reported procedure[4)] gave a lactone **1**. Hydrolysis of the lactone **1**, subsequent esterification with diazomethane, and treatment with dihydropyran afforded a stereoisomeric mixture of pyranyl ethers **2** in 56% yield, MS m/e 266 (M^+); IR ν_{max}^{film} 3030, 1740 cm^{-1}; PMR $\delta_{TMS}^{CCl_4}$ 1.16~2.00 (8H, m, CH_2), 2.45~4.04 (8H, m, CH_2O, -CH-), 3.58, 3.60 (3H, s, OCH_3), 4.50 (1H, m, -CHO-), 6.18 (2H, m, -CH). Alkylation of **2** with lithium diisopropylamide (2 equivalents) in THF-hexane and excess (2~4 equivalents) of alkyl halide at -50° for 3~20 hr. under nitrogen atmosphere yielded an alkylated product **3**; e.g. **3a** (R= CH_3), MS m/e 280 (M^+); IR ν_{max}^{film} 1740 cm^{-1}; PMR $\delta_{TMS}^{CDCl_3}$ 1.46 (3H, s, CH_3), 1.40 1.80 (8H, m, $-CH_2-$), 2.10~2.41 (1H, m, -CH-), 2.70~3.90 (5H, m, $-CH_2O-$, -CH-), 3.56 (3H, s, OCH_3), 4.15 (1H, q, J=4Hz, -CH-), 4.55 (1H, m, O-CHO-), 6.00~6.35 (2H, m, =CH). The stereochemistry of the alkyl group was deduced to be exo based on the analogy in the case of the alkylation of the adduct from dimethylfulvene and methyl acrylate.[1)] The yields of some alkylated products **3** are listed in Table. The retro-Diels-Alder reactions of **3** were carried out by



1 **2** **3** **4**

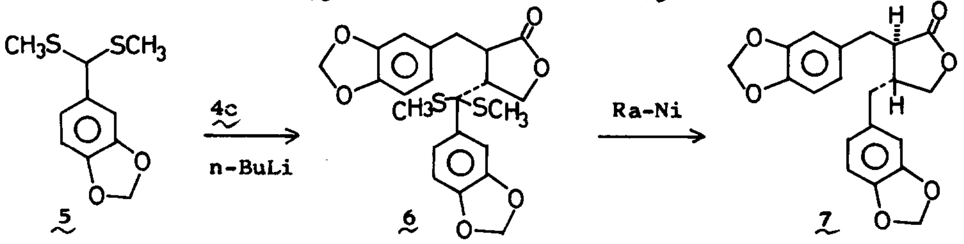
heating at 200～280° for 30 min in toluene in a sealed tube to give 2-alkyl-2-butenolactones **4**, whose spectroscopic data and the yields are summarized in Table.

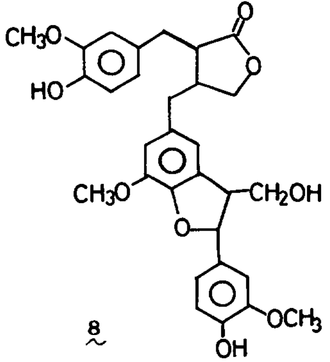
Table. Alkylation of **2** and the retro-Diels-Alder reaction of **3**

RX	**3** yield* (%)	reaction temp (°C)	MS M^+ (m/e)	**4** IR (ν_{max}^{film} cm^{-1})	PMR ($\delta_{TMS}^{CCl_4}$ 4))	yield* (%)
a. CH_3I	64	280	98	1760 1660	1.90 (3H) 4.69 (2H) 7.03 (1H)	50
b. $CH_3CH{=}CHCH_2Br$	60	280	138	1760 1660	1.71 (3H) 2.93 (2H) 4.72 (2H) 5.50 (2H) 7.05 (1H)	60
c. 	63	210	218	1760 1650	3.41 (2H) 4.64 (2H) 5.84 (2H) 6.60 (3H) 6.87 (1H)	87

* chromatographically purified products

The utility of the butenolactones was demonstrated by the synthesis of honokinin[3a)] and dehydrolappaol A dimethyl ether.[3c)] Thus, the Michael addition[5)] of the thioacetal **5** to the butenolactone **4c** with butyl lithium yielded an adduct **6** in 52% yield. Desulfurization of the thioacetal **6** with Raney-Nickel





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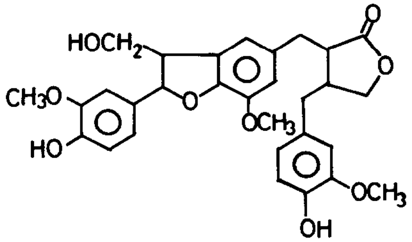

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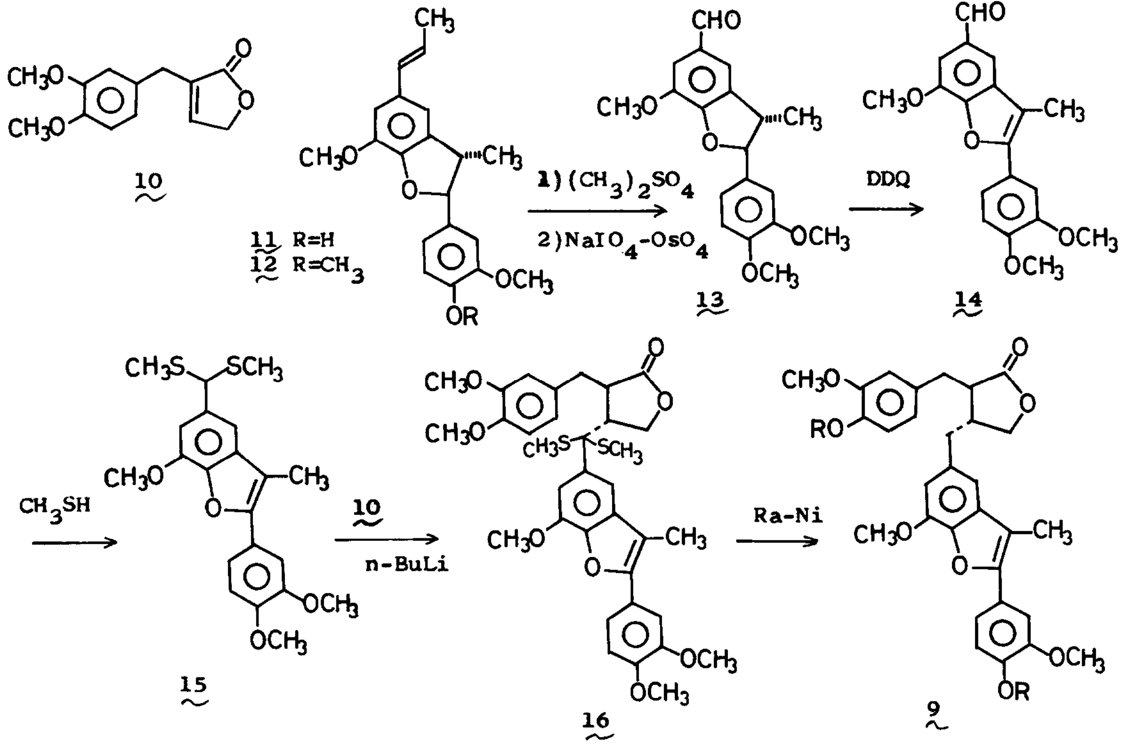
(W-4) gave (±)-hinokinin (7) (yield 40%), whose spectroscopic data are identical with those of natural (-)-hinokinin.

For the purpose of confirmation of the substituted pattern in lappaol A (8), a typical sesquilignan,6) dehydrolappaol A dimethyl ether (9), which was derived from lappaol A by acid treatment and methylation, has been synthesized according to the procedure of hinokinin synthesis. The lactone moiety 10 was prepared by the same way described above. Dehydrodiisoeugenol (11) which was obtained by oxidative coupling of isoeugenol7) was methylated with dimethyl sulfate to methyl ether 12, mp 120.8∼122.5°, $C_{21}H_{24}O_4$,8) in 89% yield. The



Lemieux-Johnson oxidation of 12 in dioxane-water afforded the aldehyde 13, mp 120.8∼122.4°, $C_{19}H_{20}O_5$ in 53% yield. Dehydrogenation of 13 with DDQ in dioxane yielded 66.2% of a product 14, mp 144.5∼145.8°, $C_{19}H_{18}O_5$. Treatment of 14 with methyl mercaptan in the presence of anhydrous $ZnCl_2$ and Na_2SO_4 in dioxane gave the thioacetal 15, mp 113.8∼114.4°, $C_{21}H_{24}O_4S_2$ in 83.6% yield. The Michael addition of the thioacetal 15 to the butenolactone 10 was carried out with n-butyl lithium in tetrahydrofuran to yield 62.3% of the <u>trans</u> adduct 16, MS m/e 638 (M^+). Reductive desulfurization of the thioacetal 15 with Raney Ni(W-4) in acetone under refluxing afforded dehydrolappaol A dimethyl ether (9), MS m/e 546 (M^+). Comparison of spectral data of synthetic material 9 with those of the derivative from natural source showed that these are identical, and clarified that so-called lappaol A consists of lappaol A (8) and isolappaol A (17) in a ratio of (3 : 2).

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References and Notes

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